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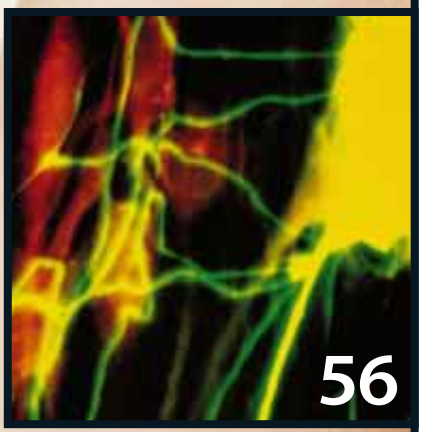

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introduction

when life knows no boun

BY MARK FISCHETTI AND GARY STIX, *ISSUE EDITORS*

Once you see the pictures, you never forget. They elicit horror, pain and, yes, a gawking fascination. An eight-year-old boy, bald with withering limbs. A nine-year-old girl stooped like a 99-year-old woman. They suffer from progeria—premature aging—and usually meet their death by the time they reach their early teens.

What's remarkable, however, is that many of these kids are happy to be alive. Some have an uncanny emotional maturity; they are cognizant of their genetic death sentence and embrace the short time they have left. Their example suggests that knowledge of one's own mortality, even at an age when the concept is normally unfathomable, can endow life with essential meaning.

The possibility of slowing the processes that cause us to age, and thereby extending the human life span, has been raised by recent scientific findings that have simultaneously provoked blistering polemics among ethicists, clergy and gerontologists. What becomes of childhood, youth, the middle years and old age if people routinely live to 150? "Don't worry, Dad, I'll go to college when I'm 30 maybe, 40 for sure. Until then, I want to drink beer with my friends. Who wants to be a wage slave for 80 years?"

The philosophers maintain that if there is no end to our existence, there is no motivation to fill it, to accomplish, to do good "before we go." They might have an argument if life were to become infinite, but it won't. Research targeted to increasing average life span isn't focused on immortality but on stretching it from 76 (in the U.S.) to 100 or even 120. If it succeeds, we'll still be inspired to live full lives.

A spate of laboratory experiments has provided clues, at the cellular level, to the processes of aging. The implications have fueled hopes that medical advances will slow our decline, extending longevity well beyond the century mark. At a minimum, the findings could lead to therapies that counter the major killers in old age, such as heart disease and cancer.

Gerontologists have a long way to go. First they have to settle on a good definition of aging. Is senescence a genetic program that kicks in once we pass our childbearing years and evolution no longer needs us? Or is it a gradual degrading of the body from daily wear and tear? We may be closing in on an answer. But even if we find the mechanisms that cause aging, that doesn't mean we will have figured out how to stop it. We know something about how cancer and AIDS work, but we haven't knocked them out. With that in mind, a "cure" for death from old age may be nothing more than mere fantasy.

Still, researchers have rounded up at least one or two likely suspects in the war on decrepitude. Oxidizing agents in our bodies, created as we metabolize food, cause our cells to degrade in the same way that rust eats away at a car. New drugs, some of which may be cousins of the vitamins we now gobble down like jelly beans, may combat the effects of these potent chemicals. A harshly restrictive diet might also slow our inevitable decline.

If any of these ideas have merit, the ethicists may find long-term job security. What would happen to society if we could all live to 100, much less 120 and up? Could it accommodate a massive population of old people? What would a "family" mean? Could we ever afford to retire? It's possible that we could manage the enormity of the upheavals if longevity crept up over time. After all, the average life span in the U.S. alone has risen from 47 to 76 since 1900. That's a 62 percent increase, and we've dealt with it.

But what if we suddenly found, say, a wonder antioxidant or some other metabolic miracle that would immediately al-

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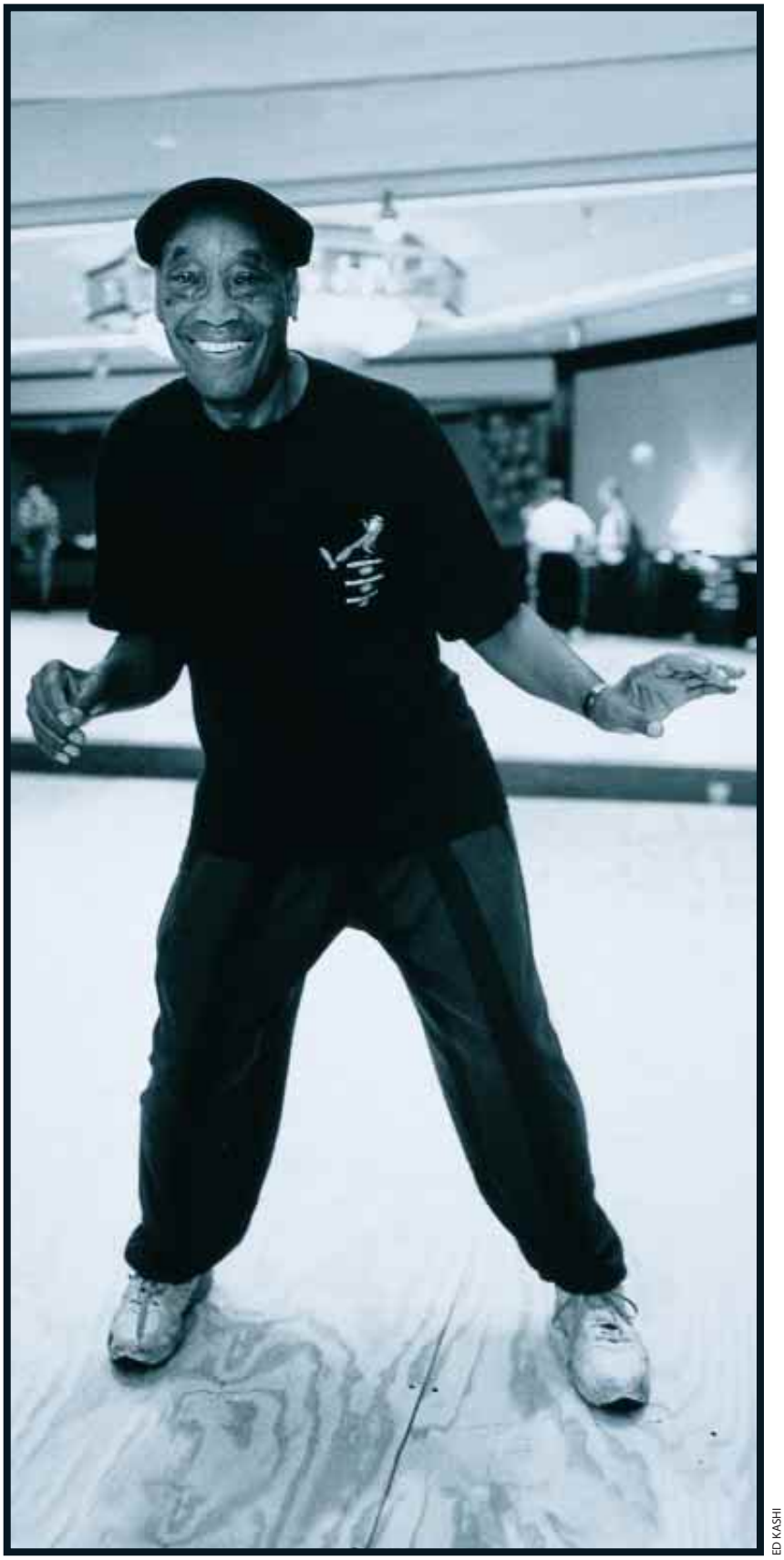
low the world to live much longer? Millions in the developed world might be able to pay for the therapy. Could the billions of poor also do so? Society could rocket toward social and financial convulsions.

That's why some pragmatic philosophers take aim at the funding of longevity research, which they say steals money that would be better spent on improving the quality of life in old age, instead of the quantity of years. But research to extend life is exactly where cures may be found for some of the most debilitating ills the elderly face: Alzheimer's, Parkinson's, heart disease, liver and kidney disease, and cancer, not to mention depression and social isolation.

The ethical arguments are important, but they may be overridden, at least in the short run, by our instincts for survival. Just ask yourself, Do you want to die next year? Probably not. Do you want to die when you're 80? "Well," you might reason, "perhaps, if I had lived a full life and was no longer in good health." But ask a 79-year-old—even a very sick one—if he wants to die "next year," and studies have shown that his answer will almost surely be the same as yours: "No thank you." Whether extra decades of life are a thrill or a bore, cheating death is a fundamental human quest. Just as certain, though, is that if the science fulfills its promise, the emerging centenarian society will transform work, family and social institutions in ways we cannot even begin to imagine.



ED KASHI

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getting ever older

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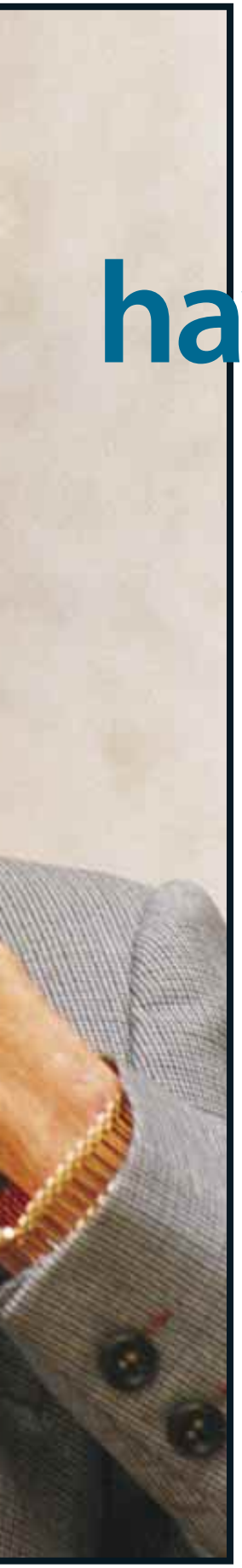

THE FIRST 150-YEAR-OLD PERSON MIGHT BE ALIVE RIGHT NOW

how long have you got?

BY KATHRYN BROWN

Forget growing old gracefully. For centuries, graying adults have tried all kinds of things to live longer: prayers, yogurt, mystical hot springs—even injections of goat-testicle extracts. Despite it all, the maximum human life span hasn't budged. At best, the statistics say, you can hope to reach about 120 years of age—and precious few actually do.

But don't throw out those birthday candles just yet. Some scientists now say they're about to trump Father Time. Working in the lab, biologists have already reared worms, fruit flies, mice and yeast that live twice as long as normal, thanks to mutations in a mere handful of genes. Other researchers are peering into the increasing molecular disorder that characterizes aging in humans, from damaged DNA to misbehaving cells. And physiologists are finding out why some people do get to celebrate their 100th birthdays. The oldest-known human, Jeanne Calment of France, recently died at 122, leaving researchers to marvel at the possibilities of long life. "Who's to say we couldn't go 10 or 20 years longer?" asks Caleb E. Finch, director of neurogerontology at the University of Southern California.

RACONTEUR: Comedian George Burns lived to 100. When asked if his doctor knew he still smoked, Burns said, "No ... he's dead."

Given the rate at which America is aging, that's a timely question. A century ago only 4 percent of the American population was above age 65. Now 13 percent is [see "From Baby Boom to Geezer Glut," on page 22]. One crowd stands out. According to the U.S. Census Bureau, the number of centenarians doubled over the past decade and may increase more than 11-fold by the year 2050. So far our seniority is mostly attributable to improved public health and modern medicine. But antiaging therapies may soon add even more candles to the cake, says zoologist Steven N. Austad of the University of Idaho. "The first 150-year-old person is probably alive right now," Austad predicts. Will it be you?

Why We Age

Ancient civilizations blamed the gods for old age. Today many scientists blame evolution, which holds that the swift hand of natural selection weeds out genes that hinder reproduction. So genetic traits that cause disease early in life, before our childbearing years, are fairly rare. While we're young, we're usually healthy and strong. "Our bodies are like rented cars," says demographer S. Jay Olshansky of the University of Chicago. "We use them up, and before things start to go dramatically wrong, we pass on our genes to the next generation."

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getting ever older

After our baby-bearing time has passed, however, our job is done. Evolution needs us no more. There are two prevailing theories about what happens next. According to the first, developed in the 1950s by British immunologist Peter Medawar of the University of London, harmful mutations of the human genome kick into gear during midlife. Because natural selection is no longer looking out for us, he reasoned, our bodies fall prey to decline and disease.

Putting a slightly different spin on life, University of Manchester scientist Thomas B. L. Kirkwood offered the "disposable soma" hypothesis in the 1970s. It suggests that the more energy you spend bearing babies, the less you have for other metabolic feats, such as defending against mutations that cause the battles of aging. If you live fast—having a lot of babies when young—you tend to die younger. Natural selection will gladly make that swap, says evolutionary biologist Linda Partridge of University College, London. In recent years scientists have fleshed out this theory, proposing that some genes act beneficially early in life yet negatively later on.

At first glance, both evolutionary images of aging seem impossible to counter. If our golden years really are determined by mutations or subtle life trade-offs, how can scientists hope to understand aging—much less fight it? The process of aging could be dominated by perhaps 36 genes, although there may be another 200 that fine-tune it, concedes Michael R. Rose, an evolutionary biologist at the University of California at Irvine. "But that doesn't mean it's impossibly complicated," he says.

In fact, Rose has already managed to assemble generations of long-lived fruit flies. In a classic experiment published in 1991, he collected and hatched eggs laid by middle-aged fruit flies. He then collected the eggs of these offspring, but only those laid late in life. On he went, repeating the process, saving only the eggs laid by older and older flies. By doing so, Rose was acting as an evolutionary force: selecting for flies that reproduced late and lived long. If a species consistently delays reproduction until later in life, over many generations, then evolution will select for traits that allow for longer life, so reproduction has the best chance to succeed. After 10 generations, Rose's flies lived twice as long as their original ancestors. "It's possible for evolution to reshape patterns of mortality," Rose concluded.

But demographer Olshansky says we shouldn't expect to see a similar phenomenon at work in humans. It would take huge numbers of older mothers who delayed childbirth—and then dozens of generations of women who did the same—for evolution to even correlate the trend with longer and healthier lives, if indeed that resulted.

Altered Genes Alter Aging

Some molecular biologists contend that these evolutionary theories are wrong altogether. They say we are bombarded with damage from daily life and genetic malfunctions across our entire genome, including the reproductive portion. That means that stopping aging lies in changing our genes. Over the past few years an increasing number of researchers have altered animal life spans by tweaking certain genes. "Evolutionary biologists would have never thought you could change a single gene and double an organism's life span, especially without decreasing fertility," says Cynthia J. Kenyon of the University of California at San Francisco. "But that's precisely what we've done."

In Kenyon's laboratory the longevity gene at hand is called *daf-2*. Worms with a mutated *daf-2* live for a month, twice the norm. Moreover, by tinkering with related genes—*daf-12, daf-16* and *daf-23*—researchers have reared worms that live up to four times longer than the normal span. Kenyon thinks the *daf* genes direct hormones that ratchet up or down a worm's rate of aging in response to environmental challenges such as food supply or temperature. And worms aren't the only ones lingering on the lab bench. Yeast, fruit flies and mice have all eked out far longer lives than normal with the aid of a little genetic manipulation [see "Of Hyperaging and Methuselah Genes," on page 68].

Researchers still debate whether aging is the cumulative result of life's tiny assaults or a more programmed series of events determined at birth. They don't know how all these genes work.

centenarians who made

Charles Greeley Abbot (1872–1973)
Determined that the sun's radiation varies.

Edward E. Kleinschmidt (1876–1977)
Teletype inventor.

Madame Chiang Kai-shek (1897–present)
Anti-Communist crusader.

BETTMANN/CORBIS (*Charles Greeley Abbot* and *Edward E. Kleinschmidt*); CHENG HUI HSU Reuters/Archive Photos (*Madame Chiang Kai-shek*)

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a difference

Irving Berlin (1888–1989)
Composer of American song standards.

Grandma Moses (1860–1961)
Folk artist, began painting at 78.

Rose Kennedy (1890–1995)
America's best-known matriarch.

CORBIS (*Irving Berlin*); ARTHUR ROTHSTEIN *Corbis* (*Grandma Moses*); CORNELL CAPA *Magnum* (*Rose Kennedy*)

Healthy habits now can add years later.

And even if they someday understand the genetic mechanisms, that doesn't mean they'll find a "cure" for aging. We know how cancer works, for example, but we haven't stopped it from commencing in people.

At present, we must be content with the few pieces of the puzzle that are starting to come together. For instance, at least four of the newfound genes affecting the longevity of lab creatures encode antioxidant enzymes. These chemicals disarm harmful oxygen molecules, called free radicals, that emerge whenever cells turn food and oxygen into energy. Like dancers looking for partners, free radicals careen within and between cells, binding to nearby molecules and disrupting normal activity. Over time, scientists suggest, this free-radical damage adds up, causing tissues and organs to deteriorate with age. This oxidizing of our bodies is often compared to the oxidizing—rusting—of metal [see "A Radical Proposal," on page 38].

Lab organisms endowed with certain extra longevity genes seem to fend off damage from free radicals and similar stresses, such as UV radiation, says scientist Thomas E. Johnson of the University of Colorado at Boulder. That molecular trick results in longer life. If researchers can reduce free radicals or boost antioxidant defenses in these animals, he adds, they may be able to design drugs to do the same for humans. "I'm confident we'll find drugs that stimulate resistance to environmental stresses and so increase longevity," says Johnson, who works with GenoPlex, a Denver company he helped to found.

Not everyone is so confident. Genes that contribute to the lengthier lives of certain lab animals may not explain aging in people at all, argues anatomist Leonard Hayflick of the University of California at San Francisco. "Humans are not big flies," Hayflick says. "To extrapolate from flies, mice and yeast to humans is utter nonsense. There are an incredible number of genes related to aging in humans that don't even exist in those organisms."

Researchers do agree that oxidative damage is only one possible cause of aging. According to a recent tally, some 300 theories of aging have been proposed—and at the very least, several key processes are involved. In addition to free radicals, for instance, aimless glucose (sugar) molecules attach to proteins, causing those proteins to link up unnaturally and change function, possibly leading to hardened arteries, tougher skin tissue, cataracts and other evils of the silver years.

Furthermore, some cells start misbehaving all on their own. After many years, somatic (body) cells stop dividing, but some don't simply die. Many apparently switch functions—often for the worse. Biologist Judith Campisi of Lawrence Berkeley National Laboratory has found that cells that give youthful skin its smooth elasticity stop dividing and then go awry late in life, breaking down the very same elasticity. "As we start to understand how this works, we have the hope of stopping these altered functions," Campisi says. This work goes hand in hand with studies of cancerous cells that won't stop dividing, as well as studies of multipurpose stem cells that could replace mature cells lost to heart disease, Parkinson's disease and other ills. [Studies on cell senescence are detailed in "Counting the Lives of a Cell," on page 50; "Mother Nature's Menders," on page 56, describes stem cell research.]

Your Number Is Up

The biochemical bits of aging may be the same for everyone, but they certainly add up differently. Your neighbor may have run a marathon at 70, while your landlord was busy having heart surgery. Your great-aunt was a

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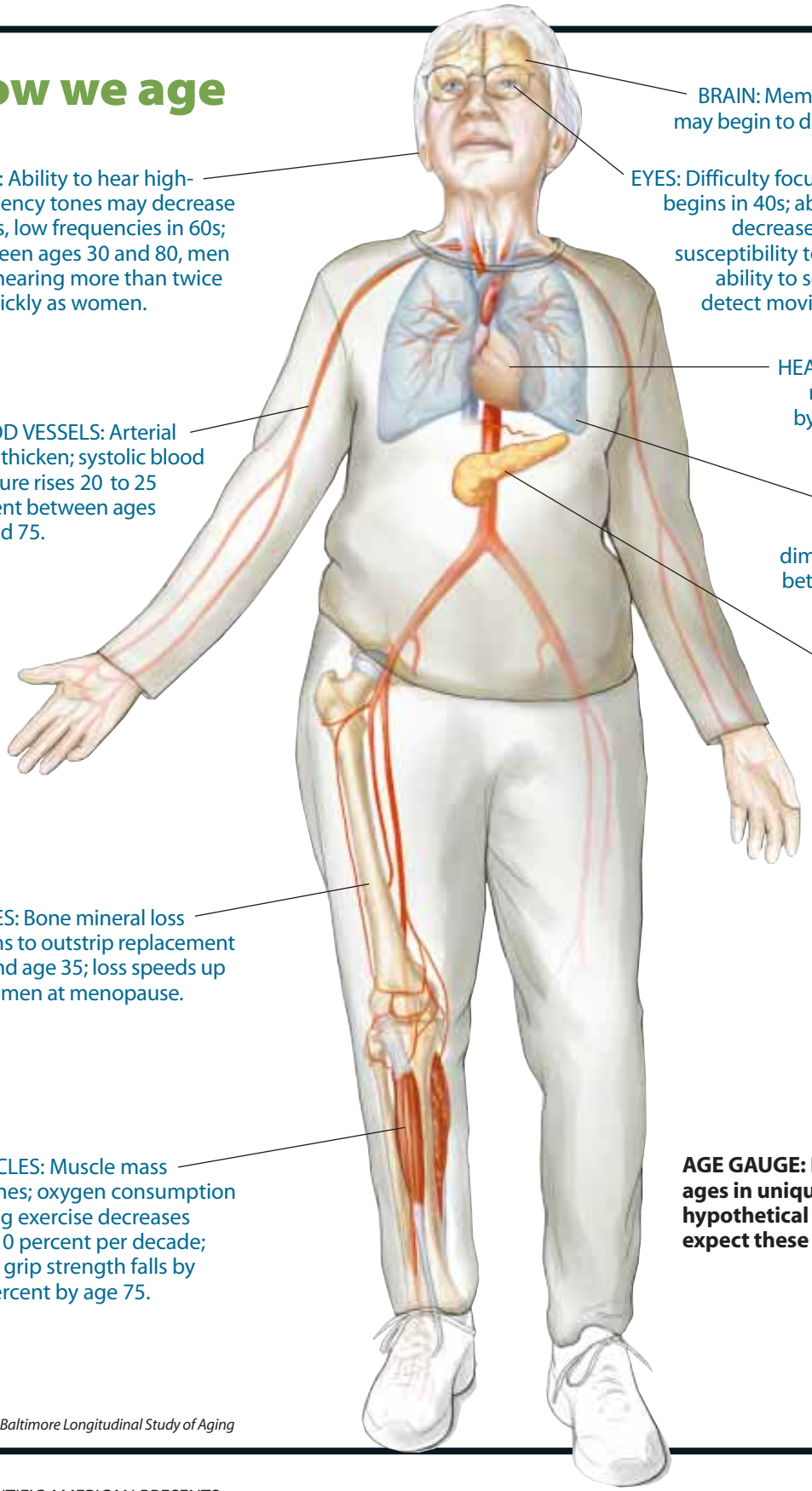
how we age



BRAIN: Memory and reaction time may begin to decline around age 70.

EYES: Difficulty focusing on close objects begins in 40s; ability to see fine detail decreases in 70s; from age 50, susceptibility to glare increases, and ability to see in dim light and to detect moving targets decreases.

EARS: Ability to hear high-frequency tones may decrease in 20s, low frequencies in 60s; between ages 30 and 80, men lose hearing more than twice as quickly as women.

HEART: Heart rate during maximal exercise falls by 25 percent between ages 20 and 75.

BLOOD VESSELS: Arterial walls thicken; systolic blood pressure rises 20 to 25 percent between ages 20 and 75.

LUNGS: Maximum breathing capacity diminishes by 40 percent between ages 20 and 80.

PANCREAS: Glucose metabolism declines progressively.

BONES: Bone mineral loss begins to outstrip replacement around age 35; loss speeds up in women at menopause.

MUSCLES: Muscle mass declines; oxygen consumption during exercise decreases 5 to 10 percent per decade; hand grip strength falls by 45 percent by age 75.

AGE GAUGE: Each person's body ages in unique ways, but a hypothetical average person can expect these changes over time.

SOURCE: Baltimore Longitudinal Study of Aging

TERESE WINSLOW

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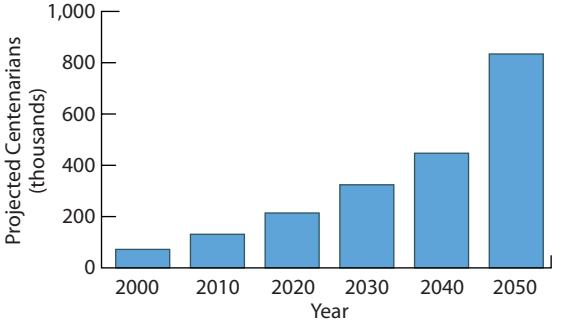
chess champion, but your grandfather couldn't remember his address. Aging is incredibly variable. "Researchers used to believe that the older you get, the sicker you get," says Harvard Medical School physician Thomas T. Perls. "That's completely wrong."

To find out what "normal" aging is, researchers with the National Institute on Aging's Baltimore Longitudinal Study of Aging (BLSA) examine the bodies and brains of volunteers every two years. The longest-running scientific study of human aging in the U.S., the BLSA began in 1958 and now has more than 1,100 active participants. The study is a snapshot of healthy aging, and yes, it does portray a gradual physical decline. As a senior, you probably won't see, hear or breathe quite as easily as you once did. But the study also suggests that life's slings and arrows aren't all outside your control. Without exercise, for example, a 30-year-old woman will lose a quarter of her muscle mass by the age of 70. But a few jaunts around the park or trips to the gym every week can fend off this by-product of aging.

Indeed, Perls says, starting healthy habits now can add years later on. Do you smoke? Keep a positive attitude? Limit red meat? The answers to such questions may affect your likely expiration date. And if you'd like to calculate that fateful moment yourself, try the Life Expectancy Calculator (www.beeson.org/Livingto100/). The tool, presented in Perls's 1999 book, co-authored with Margery H. Silver, *Living to 100: Lessons in Living to Your Maximum Potential at Any Age*, will put a number on your mortality by analyzing your answers to 23 behavior and background questions. Perls says those of us with average genes and healthy habits can expect to live until about 85.

That's pretty good—already almost twice as long as our recent relatives. Since 1900 the average life span in the U.S. has jumped from about 47 to about 76 years, according to the National Institute on Aging. It's not that we're aging more slowly. We're living longer simply because we escape many of the illnesses and events that plagued our ancestors, from death during childbirth to tuberculosis, largely because of better sanitation, cleaner water supplies and basic medical advances such as immunizations. There is new light at the end of the tunnel, too: once you creep far enough along, it

centenarian boom



RAPID RISE: By midcentury the Census Bureau predicts the U.S. could be home to nearly 835,000 centenarians, more than 11 times the number today.

LAURIE GRACE

taking it to the limit

In the good old days, aging wasn't viewed as complex. Some scientists reasoned that, like a car with a full tank of gas, our bodies arrive on earth topped off with some kind of vital substance. As time passes, our tanks drain and our bodies age. Here are a few of the notorious theories about life's limits that have emerged in modern times.

Vital humors — 19th century

Vital humors control all your bodily functions. When these humors run dry, your time is up.

Energy — 1920s–1930s

As you use energy, your cells steadily break down. The faster you live, the faster you burn energy and the sooner your demise, maintains this rate-of-living theory.

Heartbeats — 1950s

Mammals get about one billion heartbeats. As you near that limit, your heart breaks down.

DUSAN PETRICIC

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world's
oldest creatures

Hiding inside rocky crevices 1,800 feet below the Pacific Ocean, rockfish stubbornly persist well past 100 years, far surpassing their peers. Giant 10-foot-long tube worms sway in the dark depths of the Gulf of Mexico for up to 250 years. Blanding's turtles can slosh through Midwestern U.S. wetlands for at least 70 years, and certain giant tortoises push 300. Defying even greater odds, some bristlecone pines high in the California and Nevada mountains have lived almost 5,000 years!

How do these remarkable creatures do it? Scientists are trying to find out, hoping to learn more about how nature's organisms age and thus how we might lengthen human life. "The natural world offers hundreds of lessons in longevity," says University of Southern California gerontologist Caleb E. Finch.

One lesson: find an environment free of predators. Researchers have identified yelloweye and rougheye rockfish as old as 118 and 149 years, respectively, at great ocean depths. They endure partly because many of their predators prefer shallower waters, says Allen H. Andrews, a research associate at California State University. Blanding's turtles may outlive soft-shelled varieties because their rough, hard exterior deflects the bite of hungry critters, explains ecologist Justin D. Congdon of the Savannah River Ecology Laboratory in Aiken, S.C.

The record-breaking bristlecone pines have also found a safe haven; they prevail at around 11,500 feet above sea level, too high for the comfort of many insects or competing trees. One pine at Nevada's Wheeler Peak was estimated to be 4,900 years old, based on its annual growth rings, before it was cut down in 1964. Amazingly, Finch says, the trees seem to reproduce just as well in their 4,000th year as in earlier days.

For a long time, scientists didn't bother to study the longevity of animals and plants. They assumed that most creatures would die before their time because of predators, competition, natural disasters, insects or disease. But that idea is changing. To measure more precisely the effect of environment on aging and longevity, University of Idaho biologist Steven N. Austad turned to an animal that normally lives fast, breeds madly and dies young: the opossum. Austad reasoned that opossums living without the evolutionary pressure of many predators—such as owls, coyotes and wolves—would age and breed more slowly, ultimately living longer. About a decade ago he found that very situation on Sapelo Island, a scrap of land off the Georgia coast. There opossums live up to 50 percent longer than on the mainland—and actually age more slowly along the way, according to Austad's measurements of their tissues over time. Austad is now looking for similar longevity in island mice, considerably easier creatures to study in the lab.

Bristlecone pine

Galápagos giant tortoise

Yelloweye rockfish

GALEN ROWELL *Peter Arnold, Inc. (bristlecone pine)*; GERALD LACZ *Animals Animals (Galápagos giant tortoise)*; DOUG WECHSLER *Animals Animals (yelloweye rockfish)*

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Austad's research underscores the flexibility—or "plasticity"—of aging, suggesting that the right environment can increase life span. The question now at hand is: Once predators and competition are removed, do biological processes take over and cause aging in animals, even those that live a squeaky-clean lifestyle?

For clues, Austad and University of Idaho ecologist Donna J. Holmes are looking skyward. Five years ago they proposed birds as the ideal animal to use in aging studies. After all, birds are closer to humans, biologically speaking, than are worms or fruit flies, the favorite subjects of aging-study labs. They are warm-blooded, like us, so they don't lapse into periods of dormancy or hibernation, as do fish and turtles. Moreover, some birds live for decades against all odds.

This is even more remarkable because, to rev up for flight, birds generate extremely high levels of blood sugar. The 150 parakeets twittering around a basement lab at the University of Idaho have blood sugar levels so high they should be diabetic. They have elevated temperatures and burn energy at feverish rates. Yet they live to 20, old for parakeets. These bird traits defy a primary theory of aging—that increased metabolism creates higher levels of oxygen molecules, called free radicals, that oxidize cells, damaging tissue in ways normally associated with aging. Rather than rapidly growing weak and dying, birds carry on in good health, year after year.

In 1998 Holmes, Austad and their colleagues reported that the cells of three bird species—canaries, European starlings and budgerigars (a.k.a. parakeets)—can endure a battery of oxidative stresses with surprisingly little damage. The scientists exposed these bird cells, along with the cells of mice, to baths of hydrogen peroxide, bolts of radiation, chambers of oxygen and doses of pesticide. Under these assaults, the DNA inside the mouse cells often unraveled, broke or stopped replicating, typical signs of free-radical damage. The bird cells, on the other hand, divided normally and repaired much of the induced DNA damage right away. "We don't have any idea yet how the bird cells are doing it," Holmes says. "But it appears that birds have special enzymes that dispose of free radicals. If free radicals are a primary mechanism of aging, then this may explain why these birds live so long."

If the scientists find the genes responsible for birds' resistance to free-radical damage, they might someday apply them to humans. "Ultimately," Holmes continues, "it's possible that gene therapy could transfer a gene from the bird genome to the mammalian genome." As U.S.C.'s Finch puts it, "We're in a major discovery phase now." If researchers can understand the endings of other species, we just might learn how to rewrite our own. —*K.B.*

seems, your chances of dying actually begin to ease. Demographers have found that death rates steadily climb until about 85—and then begin to slowly edge back down again. The same phenomenon holds true for some fruit flies, wasps, worms and yeast in studies led by researcher James W. Vaupel of Duke University and the Max Planck Institute for Demographic Research in Rostock, Germany. It's as though we all decline to a certain point, rest, get our second wind and rally back.

And some people *really* rally. As the number of centenarians in the U.S. climbs, scientists hope to learn the secrets of their success. Already Perls has a few hints, gathered as head of the New England Centenarian Study, which tracks more than 450,000 older adults in Massachusetts to see who reaches 100 and why.

So far 169 centenarians have participated in the study; there is data on 250 others. They are a motley crew: Some exercise. Some smoke. Some brazenly defy the notion of a healthy lifestyle. Nevertheless, almost all have lived free of cancer, and up to a fourth have escaped any form of dementia.

How do they do it? With luck—and a few "genetic booster rockets," Perls says. Studying half a dozen families that include 10 or more centenarians, he is closing in on chromosome regions with genes linked to long life. Isolating the genes won't be easy, but drugs to mimic their effects could one day prevent some deadly diseases of old age. "In the future, we may be able to look at your genetic profile, determine your risk for various diseases, and give you vitaminlike pills to delay or prevent those diseases," Perls forecasts. Blessed with centenarian-style health, you too may live to well over 100. ["Design for Living," on page 18, relates more about what scientists have learned from studying centenarians.]

Whether you will live *many* years beyond 100, though, remains to be seen. No one knows when or how scientists might extend our life spans. It's been more than 60 years since researchers first discovered that lab animals that consume fewer calories than normal—a regimen known as caloric restriction—tend to live unusually long. But scientists still don't know how caloric restriction works or if it can slow aging in humans [see "The Famine of Youth," on page 44]. There are other dilemmas as well. Could the U.S. afford legions of elderly people? Would you be alive but ridden with ailments at age 130? At 150? "This research raises all kinds of ferocious social and economic questions," University College's Partridge observes.

We just might find ourselves answering these questions. "People tend to underestimate how fast the aging field is moving," claims biologist Leonard P. Guarente of the Massachusetts Institute of Technology. "We're uncovering the molecular basis of aging. No, we're not at a point where we can intervene in humans yet. But we have every reason to be hopeful that day will come."

Kathryn Brown *is a writer at* Science News.

Further Information

Life Expectancy Calculator can be found at www.beeson.org/Livingto100/ on the World Wide Web.

Why We Age. Steven N. Austad. John Wiley & Sons, 1997.

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ROBERT RICCI *Liaison Agency*

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sign for living

BY POLLY SHULMAN

Jeanne Calment had the longest memory in human memory. As recently as 10 years ago, she recalled a trip she took to Paris where she saw an impressive new structure going up—the Eiffel Tower. Vincent van Gogh used to buy paint at her family's shop in Arles, and the artist made a bad impression on young Jeanne: he was ugly, bad-tempered and reeked of alcohol, she told reporters years later. At 85 she took up fencing and at 120 gave up smoking—"It was becoming a habit," she explained. She outlived all her descendants, including her grandson, a doctor, who died in 1963. Asked at 115 how she saw her future, she quipped, "Short. Very short." But she was wrong: she lived seven more years, dying on August 4, 1997, at 122 years, five months and 14 days, the longest verifiable life span of any human being. She attributed her long life variously to olive oil, wine and a sense of humor. "I have only one wrinkle," she said, "and I'm sitting on it."

Most of us, of course, can never hope for longevity (or humor) to match Calment's—she's one in six billion, points out Thomas T. Perls, acting chief of gerontology at Beth Israel Deaconess Medical Center in Boston. But the number of centenarians is rising every year. According to a July 1999 census report, there are about 72,000 people older than 100 in the U.S., a number expected to reach 834,000 within the next 50 years. Even more important, says Richard M. Suzman, associate director for behavioral and social research at the National Institute on Aging, the rate of disability in all populations, including the oldest old, has been dropping since 1982. Demographers, geneticists and medical researchers hope that studying healthy people in their 80s, 90s, 100s and beyond—"the superstars of longevity," as Perls refers to them—will yield vital clues to how all of us can live longer, healthier lives.

FOR THE RECORD BOOKS: Jeanne Calment, whose life was the longest ever documented, here contemplates the world from the vantage point of 121 years, a year before her death in 1997.

To Leonard W. Poon, principal investigator of the Georgia Centenarian Study, the secret to longevity is that there is no secret. Poon and his colleagues followed 144 cognitively intact, independently living centenarians, whom he calls "the cream of the crop." Some were compared with groups of people in their 60s and 80s from similar backgrounds; others were interviewed and tested every six months for what remained of their lives. He believes the most important lesson of the study is the qualities that stood out among the oldest old.

For example, few of the centenarians in the study smoked, were obese or drank heavily. They remained active throughout life, ate breakfast regularly, and consumed plenty of vitamin A and carotenoids by eating fruits and vegetables. "In terms of psychology and attitudes, they've resolved whatever issues they have, they're sure of themselves, and they want to have their way," Poon says. "They would not take your word for anything—they want to find out for themselves. And they're very protective of themselves." Learning about the diversity of characteristics that centenarians share, he thinks, "isn't a bad result, because anyone can find one factor rele-

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getting ever older

vant to their lives, one thing that's possible to change. The diversity gives all of us hope to be able to live longer."

Poon, a psychologist by training, considers motivation and attitude as important as genes. But Perls, director of the New England Centenarian Study and a co-author of *Living to 100,* believes there are genes that can guarantee their lucky recipients a better chance to live a long, healthy life, and he means to find them. Siblings of centenarians in his study, he points out, have a five times greater chance than average of living to their early 90s and a 15 times greater chance of living to 100. Of course, siblings share environmental factors as well as genes. Could some of these be responsible? "Is it the chicken soup their mom makes?" Perls asks. "No, because their parents also live unusually long."

MARK HAVEN

WHAT'S HIS SECRET? Artist Harry Shapiro, who is 100 years old, is an Ashkenazi Jew, a group being studied in a search for longevity genes.

Along with medical and population studies, the New England Centenarian Study does genetic work with centenarians in collaboration with molecular geneticists. The scientists look for longevity genes in families with a high proportion of members who live to extreme old age, such as a group of seven siblings, five of whom passed the 100-year mark. (Calment's family is another good example: her father died at 93, her mother at 86.) People in the past thought there were tens of thousands of genes that had a weak effect on longevity, but Perls and his colleagues believe there are probably just a few genes with very strong effects: "When you see the kind of clustering [of people] we're seeing, mathematically it's got to be only a few genes—maybe just 10 or so. In one family, you may find one or two." His team is very close to finding regions of chromosomes, he says, that contain such genes. Right now they're checking their results. "It's such a big-deal finding, we want to make sure we're correct. Once you find a region, you know everyone and his grandmother is going to be falling all over themselves to find the genes on that region."

Nir Barzilai, a gerontologist at the Albert Einstein College of Medicine who collaborates with Perls's group, is looking for longevity genes as well. He and his colleagues study "founder populations"—small, genetically isolated groups that gradually expanded to large numbers, all the while marrying within the community. One collaborator hunts through the genes of the Amish; Barzilai does the same with Ashkenazi Jews. The fact that members of such groups share large amounts of genetic material makes it easier to find relevant genes. The geneticists compare the genes of long-lived group members with those of members with short or normal-length lives. Because these people have so much genetic material in common, any genes found in the long-lived group but not in the short- or normal-lived group have a good chance of being the ones the scientists are looking for.

But once they find them, what good will it do the rest of us? If we're not blessed with lucky genes, should we throw up our hands and write our wills? Of course not, Barzilai says. The whole point is to find out what functions those genes perform, then develop medicines to mimic them. "If they have to do with oxidation, we'll try to manipulate oxidation. If they increase levels of HDL—that's the beneficial kind of cholesterol—maybe we can increase HDL. Here's another example: I had a 102-year-old who had a very high grade cancer, with a prognosis of two months, but she lived with it for five or six years. Maybe something in her genes protected her from this cancer," Barzilai notes. If so, understanding how that protection worked could help doctors develop cancer-fighting drugs. The genes will also shed light on healthy behavior. If centenarians have genes that keep them slim, the rest of us could try to mimic that by cutting down on the excess calories, as Perls does (his work with the very old has inspired him to shed 15 pounds).

Although it's too soon for genetic results in their study, Barzilai and his team have been quizzing their centenarians for shared characteristics. Like Poon, they've found a lot of diversity. "No one of the centenarians is telling me that he did anything special to reach that age," Barzilai says. "Many of them ate what they shouldn't have eaten, or they smoked. But one thing they seemed to have in common was some form of flexibility. Many of them had very hard lives. They rolled with punches, got up and continued with a good attitude."

One tough problem is to separate

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cause from effect. Did Barzilai's and Poon's centenarians live longer because they rolled with the punches, or did 10 decades of experience give them the wisdom to accept experiences that would have thrown them for a loop in their youth? Centenarian researchers would like to go back in time and interview their subjects at 20, 50, 80—but of course, they can't.

Butterfat for Couch Potatoes

Poon's centenarians got plenty of vitamin A and ate breakfast regularly. Well and good; Mom, your doctor and your cereal box would approve. But they also drank more whole milk and were less likely to avoid cholesterol than the 60- and 80-year-olds in the study. Is butterfat good for you? Or did they have genes that protected them from its deleterious effects, as Perls believes? "The centenarians in our study don't have a history of exercise, but the rest of us can't get away with this," he says. And what about Calment's cigarette habit? Do genes make smoking safe for some of us but deadly for others?

Such questions are important not only on an individual level but also demographically. Understanding and predicting changes in the general population and the health statistics of older people will be increasingly important to policymakers and health care providers as well as to aspiring centenarians.

The demographics of the oldest populations may yield some surprises. A study conducted at Odense University in Denmark, analyzing mortality data from 13 European countries and Japan, showed that after age 97 a person's chance of dying at a given age slowed from the expected exponential growth trend. Indeed, many diseases strike preferentially at earlier ages. Rates of many cancers decline after 85, as does the chance of developing Alzheimer's disease, particularly for the 25 percent of Americans who have at least one copy of a gene type predisposing them to it.

On the other hand, the incidence of other major diseases increases with age. And the very old, whose immune systems have weakened with age, are more susceptible to some common infectious diseases, such as pneumonia and flu. In fact, for most of the elderly population, Suzman argues, mortality goes up, and the prevalence of disability and chronic diseases also increases with each additional year of age, although the rate of increase does seem to slow down sometime past 90.

One factor that sheds both light and confusion on the question of what the oldest Americans will be like in upcoming decades is the cohort effect. Groups born in different decades have very different patterns of mortality and survival, Suzman says, which can be difficult to tease out. For example, levels of education that Americans attain have been rising with every generation. Increased education improves their life and health expectancy—although why is a big mystery. Part of the explanation is that education affects income level, which affects health.

THE SENTINEL

AND THE WINNER IS ...114-year-old Eva Morris of England, who is currently the oldest person alive, according to the *Guinness Book of Records.*

Education may also encourage people to adopt healthier lifestyles. More highly educated people may end up in jobs that are less stressful, or education may allow people to deal better with the rigors of stress. "It may have an impact on the brain, and the brain may turn out to be the major arbiter of survival, rather than the coronary artery," Suzman observes. And education is only one of dozens of factors that vary dramatically from one decade to another, including nutrition, smoking, sun exposure and exercise.

How much, for example, does medical care affect mortality? "Oddly, that's never been effectively measured," Suzman says. Medical intervention will have an increasing impact, he believes, sometimes through information produced by medical research, rather than medical treatments. Convincing Americans to get off the couch and shed excess pounds, for instance, could have a huge impact. So could new methods of disseminating information, such as the Internet. "Life expectancy is the least of it," Suzman says. "More important is health expectancy."

Calment notwithstanding, most of us have genes that will take us to 85 or so, barring physical catastrophe. But our behavior can help reduce or eliminate chronic diseases that make the last years painful for many. And geneticists are planning to search the genes of centenarians for clues not only to killer diseases but also to diseases you can live with but may not want to—things like macular degeneration, Barzilai says, or hearing loss. "Sans teeth, sans eyes, sans taste, sans every thing," moaned Shakespeare, describing the last years of life. Thanks to centenarians, the future may not need to be like that.

Polly Shulman *is a freelance writer in New York City as well as the great-granddaughter of a centenarian.*

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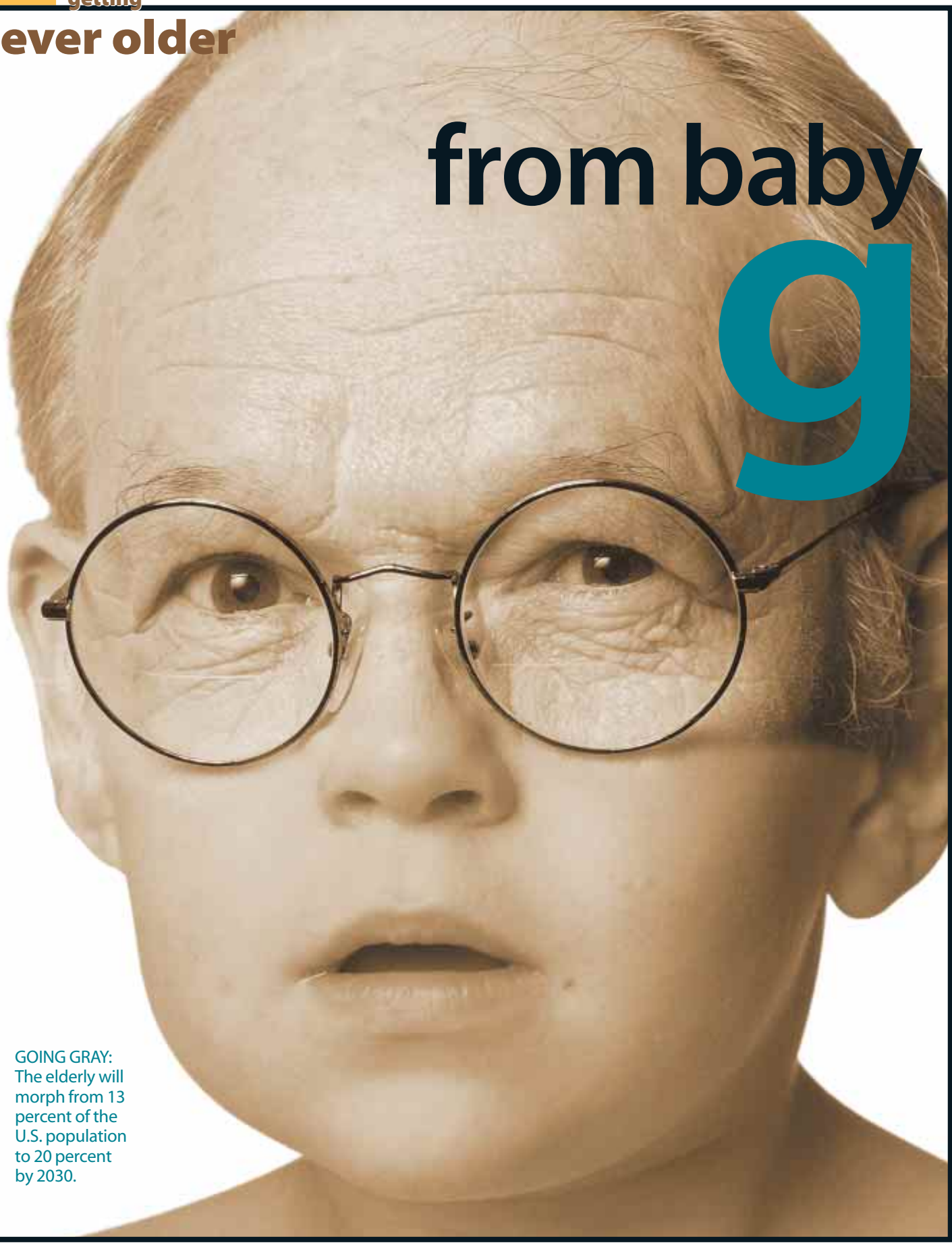

GOING GRAY: The elderly will morph from 13 percent of the U.S. population to 20 percent by 2030.

SLIM FILMS

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BY 2030, ONE IN FIVE AMERICANS WILL BE A SENIOR CITIZEN

boom to eezer glut

BY J. R. BRANDSTRADER

Want to put a face on the demographics of aging? Meet Mary Kikukawa Fichter, who's 93. Age has largely silenced this educated mother of seven, but she still manages a smile when her son, Joe, presides over a rousing game of Trivial Pursuit for her and her friends. Mary, who was born in the U.S. in 1906 of Japanese and Irish parents, lives in a nursing home in northern New Jersey. Her roommate is a friend of 40 years, but Mary can no longer remember her name. Joe calls the place "a bus stop for people waiting to die." Remembering his mother's voice from an earlier time, he talks about the inevitability of her passing: "I know she'd welcome it." Whether Mary's age is a result of healthful habits, relative wealth or just plain luck, she shares ancestry with the demographic group with the longest life expectancy in the country—Asian-American women.

Today Mary's age is exceptional, but her present may become the normal future for baby boomers. The millions of people born between 1946 and 1964 now create a bulge in the U.S. population between ages 36 and 54. In another decade the first men and women who hoped they died before they got old (to quote rocker Pete Townshend) will turn 65. From that watershed forward, the number of U.S. elderly will swell from 13 percent of the population to 20 percent by 2030. The baby boom will become a geezer glut.

The sheer numbers mean many more people will live to a very old age. But American life expectancy is far from the highest in the world, ranking 21st globally. According to the U.S. Census Bureau's International Programs Center, the life expectancy of a U.S. citizen born in 1996 is 76, a few years behind most European countries, Canada, Israel and Singapore. Japan is the champ at 80. "Our infant mortality rates are somewhat higher than those in northern Europe and Japan," says Bob Anderson, a senior statistician at the National Center for Health Statistics. "And that makes a big difference."

Vagaries lie behind some of the numbers. For instance, children in Japan who are born alive but die within a few hours are counted as fetal deaths, not infant deaths, reducing the country's infant mortality figures and thus raising the average life expectancy. Other differences have clear causes; northern Europe's health care system "doesn't do quite as well as our system at the oldest ages," Anderson explains, "but it does much better at the youngest ages," improving overall life expectancy.

Life expectancy has climbed significantly in the past century. Census Bureau analyses show that in 1900, the average life expectancy across the planet was less than 30 years. By 1950 it had climbed to 46. By the late 1990s it was 66. By 2050, projections indicate it could be 76. A large part of the increase has been attributable to safer childbirth for babies and mothers and declining fertility rates, lowering the incidence of infant deaths, which tends to drag down the average life expectancy in a population. Simple public health measures such as cleaner water, sanitation, antibiotics and basic immunizations account for much of the rest, eradicating widespread killers such as diphtheria and polio in the developed world

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percent of population over age 75 in 1996

ELDER EARTH:
The ranks of the oldest old (age 75 and up) vary widely among nations but will have increased significantly in many countries by 2025.

and holding them in check elsewhere. Only in recent times has modern medicine significantly lengthened the years people can expect to live once they reach middle age.

Closing the Gender Gap

Living in a prosperous country is no guarantee you will reach Mary's age, however. A study called the U.S. Burden of Disease and Injury, by the Harvard School of Public Health, found a staggering 40-year gap between the longest-lived Americans—Asian-American women—and the shortest, Native American men. Asian-American women like Mary are outliving even Japanese women. But Native American men in Bennett County, South Dakota, have the life expectancy of a copper miner in AIDS-ravaged Botswana, which has one of the lowest life expectancies on earth.

Don't let averages raise your hopes or fears too much, though. Plenty of people diverge from the odds. A life expectancy of 76 applies to no real group, not even actual U.S. babies born in 1996. Average life expectancy is a statistical concept, not a predictor of how long a particular person will live. "Life expectancy figures can speak to some general cultural trends," says James Walsh, an expert in actuarial and risk management and author of *True Odds: How Risk Affects Your Everyday Life*. "They do not speak to whether you, who drink half a fifth of gin a day and smoke a pack of cigarettes, are going to live to 80."

Nevertheless, mortality statistics tell us that in general, boomer women, unlike their great-great-grandmothers, have a better chance than their guy pals of getting that 100th birthday party. At the beginning of this century, men outlived women in many countries. As a result of better childbirth methods, women have caught up, adding more than 30 years to their life expectancy during the 20th century. Men have added years, too, but the higher rates of smoking and occupational hazards among men during most of the 1900s slowed their progress as compared with women. Today women in developed countries outlive men by about six years. Men still live longer in a few areas where women's social status is low and maternal mortality is high.

Interestingly, the gender gap is now closing in the U.S. Men's life expectancy is rising faster than women's because heart disease has been declining at a faster rate for males than females. At the same time, the incidence of lung cancer in females is rising faster than in males. "Women didn't really start smoking until the 1950s or 1960s," Anderson says. "They are feeling the effects now, whereas men have already

leading causes of death in the U.S.

1900	1997
1. Pneumonia and flu	1. Heart disease
2. Tuberculosis	2. Cancer
3. Diarrhea and intestinal ills	3. Stroke and brain lesions
4. Heart disease	4. Lung disease
5. Stroke and brain lesions	5. Accidents
6. Kidney inflammation	6. Pneumonia and flu
7. Accidents	7. Diabetes
8. Cancer	8. Suicide
9. Senility	9. Kidney inflammation
10. Diphtheria	10. Liver disease

NEW THREATS: Clean water and immunizations have reduced basic killers, leaving room for others to rise.

SOURCE: CENTERS FOR DISEASE CONTROL AND PREVENTION

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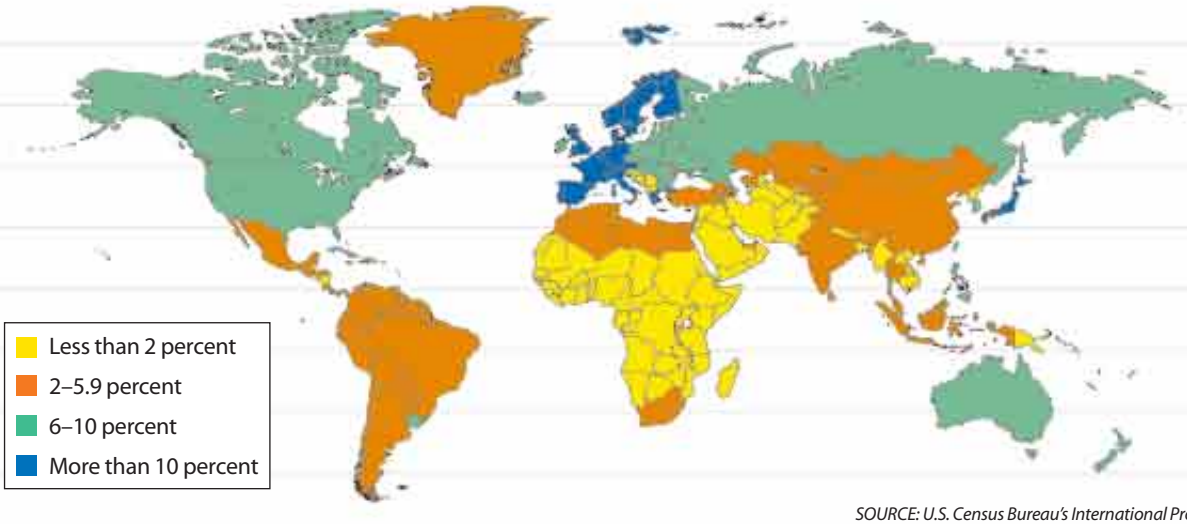
over age 75 in 2025



SOURCE: U.S. Census Bureau's International Programs Center

LAURIE GRACE

had that effect and are beginning to quit." As women behave more like men, they die more like men.

Improving life expectancy among U.S. males is also driving the nation's overall life expectancy gains. Life expectancy of a 65-year-old male in 1995 was 15.5 years, but it promises to climb to 20 years in the first half of this century, according to median Census Bureau projections. The bureau's rosiest calculations indicate that the life expectancy of some of the later boomers could hit 25 years by the time they reach 65.

Poverty Hurts

Everything from income and diet to occupation and bad habits can move people off the average curve. Poor, uninsured people have only minimal health care and succumb to disease sooner than average. Drug overdoses, alcoholism and suicide are all factors in the early demise of many rock musicians. Nationwide, the Bureau of Labor Statistics says, highway crashes are the leading cause of on-the-job fatalities. And left-handed people appear to be more prone to premature deaths than righties are.

Although such factors may sound haphazard, they can coalesce within certain demographic groups. "The classic case is among black males in the United States," Walsh says. "They have a lot of really bad life expectancy stressors at the beginning of life," including high child mortality, tuberculosis and homicide, which are exacerbated by poor medical care, overcrowding and poverty. Young black men die at a rate disproportionate to other demographic groups. Ironically, Walsh says, "if a black man lives to 40, his life expectancy can increase because he has kind of made it through the early hurdles." Anderson notes that one of the reasons people in Sweden live so long is because the country is economically homogeneous and has socialized medicine. At 18 percent, Sweden's proportion of population over 65 is the highest in the world.

All these comparisons and predictions must be taken with a grain of salt, however. The United Nations, which gathers international statistics, is the first to point out that global data collection can be pretty spotty, especially in regions wracked by disease, war and illiteracy. In the U.S., there are gaps in Census Bureau data, the fount of most national aging numbers. But these glitches won't stop demographers from using the figures. "The Census's numbers are statistically valid and well within the range of methodology used in most demographic surveys," Walsh says.

Even if the count were perfect, projections derived from it might not be. Every prediction includes an assumption that may or may not come to pass. What if a new bug appears and makes short work of us? After all, the AIDS epidemic threatens to slash life expectancy 10 to 30 years in southern Africa in the next decade. On the other hand, maybe scientists will figure out a way to keep us going until age 150. If they do, perhaps it would be a good move to buy shares of Hasbro; there will be a lot of boomers playing Trivial Pursuit while they pass the time at Mary Kikukawa Fichter's "bus stop"—providing a latter-day Joe comes to visit and organizes the game.

J. R. BRANDSTRADER *contributes to* Barron's *magazine and the Wall Street Journal Radio Network from New York City.*

Further Information

True Odds: How Risk Affects Your Everyday Life. James Walsh. Silver Lake Publishing, 1996.

The U.S. Census Bureau (www.census.gov) is the source of U.S. life expectancy data and collects information from countries worldwide. Also useful are www.overpopulation.com and the Population Reference Bureau at www.prb.org on the World Wide Web.

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getting

ever older

PAYDAY: Ida Mae Fuller of Ludlow, Vt., received the first Social Security check in 1940, for $22.54. She had paid only $22 into the infant system. She lived to 100 and collected more than $20,000 before her death in 1975.

SOCIAL SECURITY ADMINISTRATION

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YOU'D BETTER SAVE LIKE CRAZY IF YOU WANT TO FUND A 30-YEAR RETIREMENT

social security

BY THE EDITORS

For three generations, working Americans have thought that Social Security would allow them to retire at age 65 and enjoy the good life. That dream is now a fantasy. If you want to retire with financial security, you'd better start saving and investing heavily—now. Because although our current Social Security system has done a great job reducing elderly poverty and is currently running a $53-billion surplus, it faces a long-term funding shortfall of *trillions* of dollars.

Unless the system is overhauled, closing that gap means pushing the 12.4 percent payroll tax way up to 20 percent or more. Or cutting benefits by 30 percent. So while you're upping your savings, remember to exercise more and eat right; you may need to work longer than you've planned.

Pay as You Go

Debate over how to reform Social Security rose to fever pitch in the late 1990s and is figuring prominently in the 2000 presidential election campaign. As the number of Americans over age 65 climbs from 37 million in 1998 to 64 million by 2025, the nation will have to grapple with an imbalanced Social Security system, rising medical costs, health care rationing and age discrimination. The very nature of retirement will change.

The debate is highly emotional because Social Security is a pillar of most Americans' retirement planning. It has helped reduce elderly poverty from 35 percent of seniors in 1959 to roughly 10 percent in 1998. In that year (the latest with complete numbers), Social Security paid out $327 billion to 38 million retirees and survivors. More than 60 percent of seniors today receive most of their retirement income from the system.

Virtually no one quarrels with Social Security's achievements—or with the values they reflect. The debate is over how to sustain them as the aging of America places a wrenching strain on the system's finances.

Social Security was initiated by the Social Security Act of 1935 as a "pay as you go" system: current workers lay money on the table, and retirees get benefits from it. When the system is running surpluses, as it is today, funds not paid out are "lent" by the Social Security Administration to the government to cover the cost of other programs—everything from aircraft carriers to park rangers. In exchange, the Social Security trust funds are credited with special, nontradable debt obligations from the Treasury Department. These bookkeeping debts of one government unit to another are the only trust fund "investments" allowable by law. The funds cannot be invested, for example, in stocks or bonds. "Pay as you go" made sense in 1935, because the U.S. economy was in dire straits, and the first priority of the system's designers was to bring immediate relief to many people who had paid in little or nothing. But as more people retired over the years, the payroll taxes (or FICA, established by the Federal Insurance Contributions Act) that support Social Security's payouts had to be raised dozens of times. FICA was originally set at

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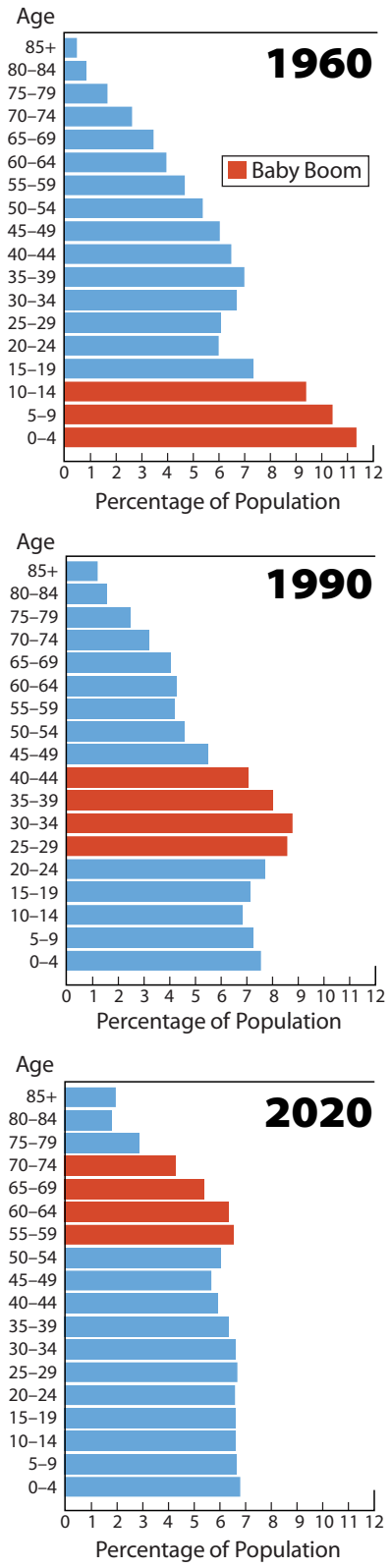
the U.S. gets age-heavy

The advancing baby-boom bulge is dramatically altering the U.S. age profile, placing a burden on the Social Security system.



LAURIE GRACE; SOURCE: U.S. CENSUS BUREAU

1 percent of all income up to $3,000. The most recent major reform, in 1983, set FICA taxes on course to this year's level of 12.4 percent. The maximum amount of a worker's wages that can be taxed—"the cap"—has also risen, to $76,200 in 2000. Given an estimated payroll of some $3.7 trillion this year, FICA taxes should produce revenues of $479 billion, more than enough to meet the needed payout of $409 billion.

The trouble is that Social Security's surpluses will evaporate. Even the $887 billion in the trust fund will not be enough to meet promised future benefits once the huge baby-boomer generation retires. The basic cause of the shortfall resides in the awesome, glacial pressures of demographics. The pay-as-you-go concept was adopted in an era of large families, rising populations and moderate life spans. When the retirement age was set at 65 in the 1930s, American life expectancy was just over 61, ensuring that there would be many active workers paying in the funds that went out to retirees.

The "support ratio" of workers to retirees has been declining steadily as people live longer, retire earlier and have fewer children. It has fallen from 42 to 1 in 1940 to 3 to 1 in 2000 and will drop to 2.5 to 1 in 2025, when millions of boomers will have retired and the nation's age profile will resemble Florida's today.

By 2014, according to the system's own trustees, Social Security will be taking in less money from FICA taxes than it is obliged to pay out—a shortfall of $21 billion a year by 2015, rising to $252 billion by 2030, in inflation-adjusted dollars.

That doesn't mean Social Security will go bankrupt. A pay-as-you-go system literally can't do that. Even with no reform, the Social Security Administration has a claim on 12.4 percent of future U.S. payroll. But from the time it goes cash-flow negative and begins drawing down its trust-fund holdings, the system's FICA income will cover a dwindling part of its obligations to retirees. By 2037 the last trust-fund assets will be exhausted, according to the latest estimates.

Without reform, this means less money for you. If, for example, you are slated to get $1,000 a month in 2037, plan on getting only about $710. The shortfall is nasty, especially for the poor.

Search for a Solution

Proposals for closing Social Security's long-term funding gap come mainly from two camps. The "tinkerers" want to raise payroll taxes, trim benefits or adopt some combination of the two. A host of policy tweaks have been floated in recent years, including lowering the inflation adjustments now made to benefits; requiring several million state and local workers now exempt from Social Security to join the system and begin paying FICA taxes; and delaying the age at which full benefits can be drawn, from 65 now to 67 or even 70, and then indexing this number up as longevity continues to rise. Another proposal is to "pop the cap"—that is, eliminate the ceiling on wages for which the 12.4 percent FICA tax must be paid. Or just raise the tax 2 percent starting right now.

All these proposals would require some pain. Not surprisingly, each one provokes furious resistance from well-funded interest groups.

The other camp, the "privatizers," wants to raise returns by investing some of Social Security's holdings in stocks and bonds, not just the nonmarketable Treasury Department obligations to which Social Security's trust fund is now limited by law.

Most of the privatizers support the creation of a national system of individual retirement accounts—like 401(k)s—that would receive some, most or all of a person's incoming FICA taxes. Each citizen would be given some degree of choice over how the money is invested. Although stock markets fluctuate, privatizers argue that over the long haul they produce significantly higher returns than government bonds do. A variant put forward by the Clinton administration would allow Social Security's trust fund to be invested in "index funds" like the Wilshire 5000, which hold stocks in thousands of U.S. companies, so that the government, not individuals, bears the risks of market fluctuations.

Whichever way the U.S. heads, it will be playing catch-up. Britain, Canada,

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Sweden, Chile, Mexico, China and dozens of other countries have either adopted or are debating national pension plans that rely heavily on investments in private capital markets. No nation—anywhere—is establishing from scratch a public pension system based on the pay-as-you-go principle, and every nation that has such a structure is facing great fiscal pressure to raise taxes, cut benefits or invest in capital markets to raise returns.

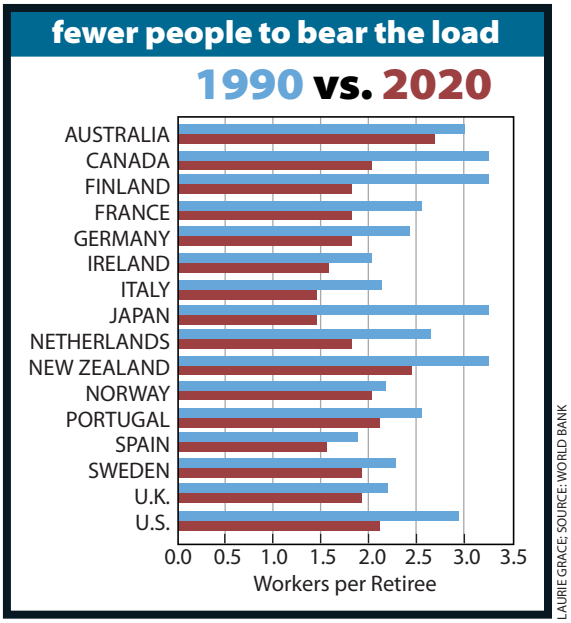
Although the financial considerations in reforming Social Security are complex, the political challenge is even more daunting. Social Security is ground zero for bitter ideological and political clashes over values. Bridging these deep emotional divides won't be easy but will be necessary to secure retirement for boomers, Gen-Xers and future generations.

Indeed, the debate over how to "fix" Social Security is a harbinger of a changing attitude toward retirement. With America's over-65 population projected to rise to more than 20 percent of the total by 2025 and with birth rates declining, an early, lengthy retirement—itself a relatively recent social construct—will soon become lore.

The percentage of 62-year-old men still working in America fell from 81 percent in 1950 to just 51 percent by 1985, but it has since begun to tick back up, past 54 percent in 1998. Similarly, half of American men aged 70 held jobs in 1950; this fell to just 16 percent by 1985 but is back up to 21 percent. With Social Security declining in power, seniors may have to work longer. And given the improvements in elderly health, they just may be more able—and more willing—to work than those a generation ago were.

What's more, with younger workers in short supply, sustaining the American economy's extended "boom" will depend on more seniors in the workforce. Conveniently, the shift to a service economy means that there are more highly skilled and less physically demanding jobs for seniors to compete for—or just hang on to. Longer-term, it's not hard to envision millions of seniors planning to use their mid-60s—following their "first retirement"—to go back to school and retool before pursuing a second or third career, whether full- or part-time. Society may well come to see the elderly as an underutilized resource, and many boomers will want to keep a hand in the work of society, maybe well into their 80s.

SHORT SUPPORT: The ratio of workers to retirees will drop sharply in many countries, forcing reform in public pension systems worldwide.



LAURIE GRACE; SOURCE: WORLD BANK

Perhaps legislation to remove the "earnings penalty" on benefits, which President Bill Clinton signed in early April, will help encourage more people to stay in the workforce longer. Under the Senior Citizen's Freedom to Work Act, people between 65 and 70 will no longer lose $1 of their Social Security benefits for every $3 they earn above $17,000 a year.

The rising percentage of seniors and their high voting rate virtually assure that politicians will be offering both the elderly and their employers new incentives to work longer. That's something of a rosy scenario for well-heeled, well-educated seniors. But further down the financial food chain, millions of seniors who lack private pension coverage or personal savings—roughly half the elderly population—may have to bid for less lucrative "second careers" as checkout clerks or night guards.

What You Can Do

The best thing you can do to shield yourself against possible future shortfalls in Social Security is to step up all forms of savings to cover a "worst case" gap in what the system will be able to pay you.

A first step is to visit the Social Security Web site. There you can request a form for getting a statement of all of your past Social Security payments and your projected monthly benefits, adjusted for inflation (see www.ssa.gov/top10.html). Once you have returned the completed form, the administration will send you a free report that details every penny you've paid in FICA taxes and the projected monthly benefit you can look forward to (adjusted for inflation).

These data will give you a sense of your worst-case shortfall. As in the earlier example, if your inflation-adjusted monthly payout will be $1,000 a month, you live past the year 2037, and nothing is done to improve Social Security's return, you can expect to receive only 71 percent of your benefits. So at a minimum, you should plan now to invest enough to provide you with an additional, inflation-adjusted $290 per month—indefinitely.

Note, however, that this amount of savings and investment will just cover your Social Security shortfall. Your monthly check will not be enough to live on comfortably. You'll need to create further income streams with every form of personal and pension savings you can muster. Social Security benefits were never intended to cover all the financial needs of all retirees. The money was, and is, meant to be only a base.

Further Information

Opposing views of how to manage Social Security can be found at **The Heritage Foundation** (pro-privatization) at www.heritage.org; and at **The Economic Policy Institute** (anti-privatization) at http://epinet.org on the World Wide Web.

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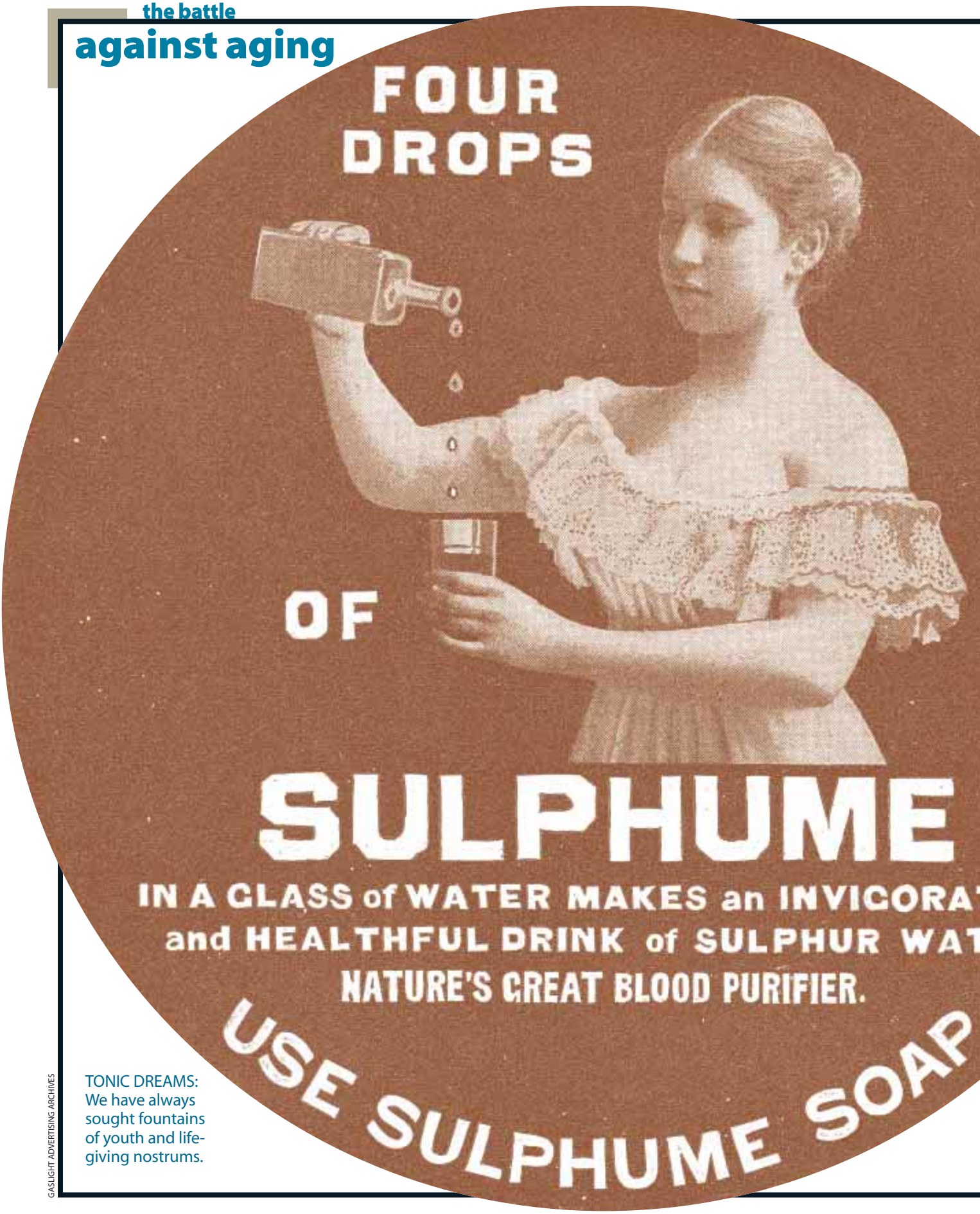

GASLIGHT ADVERTISING ARCHIVES

TONIC DREAMS: We have always sought fountains of youth and life-giving nostrums.

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THE ELIXIRS DU JOUR—ANTIOXIDANTS, GENE THERAPY AND AEROBIC CONDITIONING—HAVE YET TO PROVE THAT THEY DO MUCH BETTER THAN THE POTIONS AND PATENT MEDICINES OF YESTERYEAR

living longer: what really works?

BY ROBIN MARANTZ HENIG

A *New Yorker* cartoon shows two old geezers creaking in their rocking chairs on the front porch. "I don't want to live forever," says the male geezer to the female geezer. "But I damn sure don't want to be dead forever, either." We may not want to live forever, but how about for a long, long time? How about for 200 years or 300—two or three times the age that is now considered the outer limit of the human life span? A longer spin on this earth is apparently something that appeals to many of us, but as the checkered history of aging "cures" makes clear, it remains an elusive goal.

Advice abounds about how to beat aging, by which we usually mean either living to the age of 150 or more or staying youthful while living out a life span closer to the biblical threescore and 10. Some of the methods promoted over the years have sounded like sorcery: sleep with virgins, drink the blood of virile youth, get injections of a concoction derived from the testes of dogs and guinea pigs. These techniques have done nothing more than line the pockets of the people hawking them.

Today more temperate sages offer the same advice our mothers did: eat and drink in moderation, exercise regularly, get enough sleep. All boring, and only marginally effective. Good health habits can make you leaner, more aerobically fit and less liable to suffer some of the worst ravages that aging brings—but they won't keep you young, and they won't make you live much longer than you were genetically programmed to live.

The advice that is really getting people excited these days sounds much more scientific, derived as it is from what we are learning about how cells age, how that relates to organisms' aging and how the process can be forestalled. But even these techniques—hormones, antioxidants, gene therapy, calorie restriction—have not been proved conclusively to make any difference in how long you will live or how well you will age.

It's true that some laboratory animals who have been exposed to a few of the latest rejuvenating compounds have indeed lived longer—on average,

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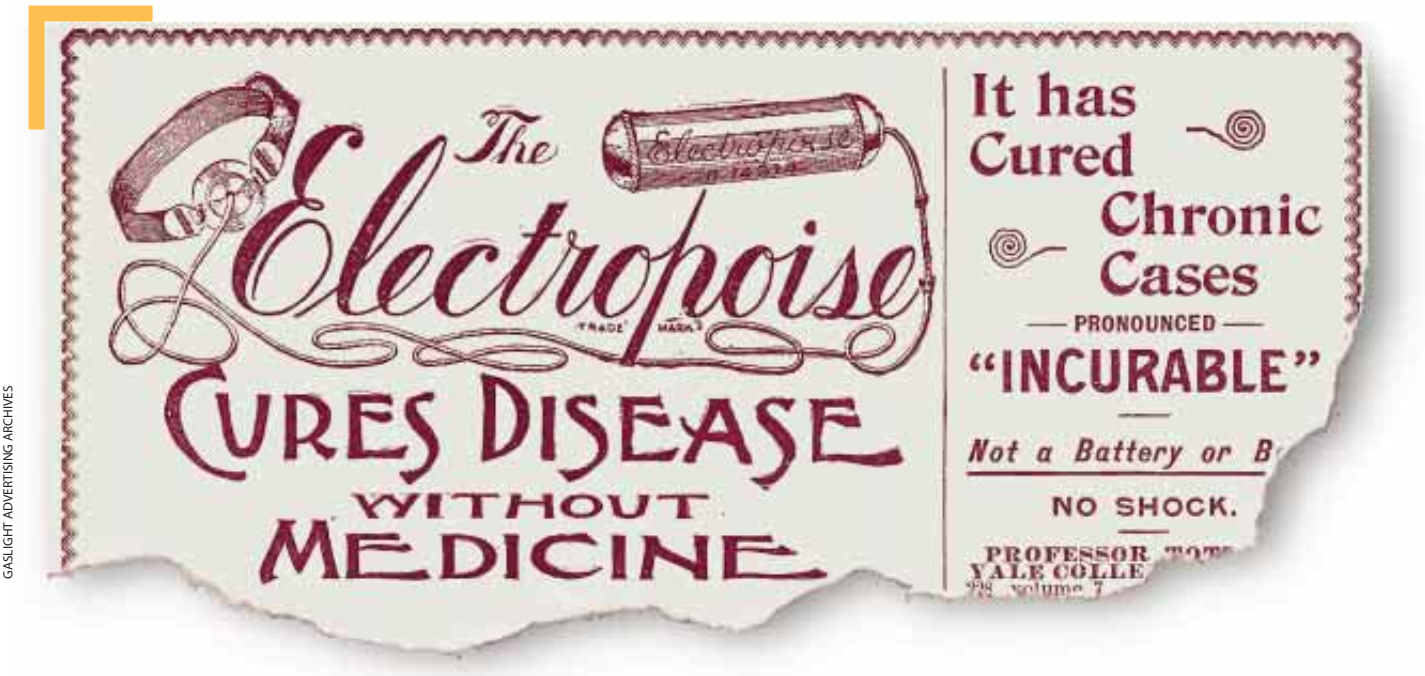

GASLIGHT ADVERTISING ARCHIVES

from 40 to 100 percent longer when treated with melatonin or calorie-restricted diets. But this does not necessarily translate into a human life span that is 40 to 100 percent longer. As far as gerontologists are concerned, people cannot live beyond the limit of about 120 years, with the occasional exception, such as Jeanne Calment, who was 122 years old—and had the birth records to prove it—when she died in 1997. You and your grandchildren, and probably your great-grandchildren, will almost surely die before you reach that limit. But you, and certainly they, are more likely than any previous generation to achieve a life span of close to 120 years. In other words, scientific progress will enable a greater proportion of the population than ever before to live out the human life span to its fullest.

Centenarian Tsunami

According to the U.S. Census Bureau, more than 800,000 baby boomers will have celebrated their 100th year by the middle of this century. The nearly one million boomers joining the ranks of the oldest old will constitute a swell of centenarians so substantial that the tradition of congratulating them during the morning weather report will go by the wayside. Millions more will reach their 80s and 90s.

But there is no guarantee that the last decades of those 100 or so years will be healthy ones. Today nearly half of all Americans over age 85 require some sort of help to get through their daily chores. Unless we make great strides in antiaging research, the oldest Americans of the new century may spend their last 30 years in a state of dreadful and debilitating dependency.

Such a spectacle struck horror in the hearts of the ancient Greeks—even though in their day, the average life expectancy was only 18 years. They told the story of Tithonus, a handsome young prince with whom Eos, the goddess of the dawn, had fallen in love. Unable to marry a mortal, Eos asked Zeus to grant Tithonus eternal life. He did so, and Eos and Tithonus lived happily together for many years. But Eos had forgotten to ask Zeus to grant her lover eternal youth as well. So it was Tithonus's fate to age forever. He grew weaker and smaller; he shriveled and shrank; he lost strength in his limbs and power in his voice. As he became more and more wizened, his voice reduced to a mere squeak, Eos hid him in a basket. Tithonus could get no relief from his ceaseless aging. Eventually, he turned into a grasshopper, ignored in the basket, chirping away for all eternity.

Longevity research must go hand in hand with research on the effects of aging if the result is to be of any use. These studies focus on adding years to our 120-year life span, whereas other antiaging research tries to slow the progression of decline within however many years we have. Sometimes the same intervention seems to do both things; calorie restriction, for instance, not only significantly increases the life span of laboratory animals but also makes them measurably more youthful than their contemporaries at every stage along the way. But one intervention doesn't necessarily have to do with the other. The techniques that stave off age-related declines are much further along the road to real-world usefulness than are any methods of helping humans live to be 200.

These methods might not extend the maximum life span, but they do tend to increase the average life expectancy—that is, the number of years within that maximum life span that the average person can hope to attain. When life expectancy increases, it is because medical science has concocted a way to prevent some of the catastrophes responsible for most premature deaths: infections and accidents in the younger age groups, heart disease and cancer after midlife. With the exception of infections, which require medical intervention, most of the biggest killers of adults can be staved off by healthy living. We've all heard the advice, if not from our mothers then from our doctors, our partners or our television newscasters: don't smoke; keep your weight within a normal range; eat plenty of grains, fruits and vegetables; go easy on the red meat and animal fat; drink alcohol only in

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moderation; get some kind of exercise for at least half an hour a day; put on sunscreen when you go outdoors; and wear your seatbelt.

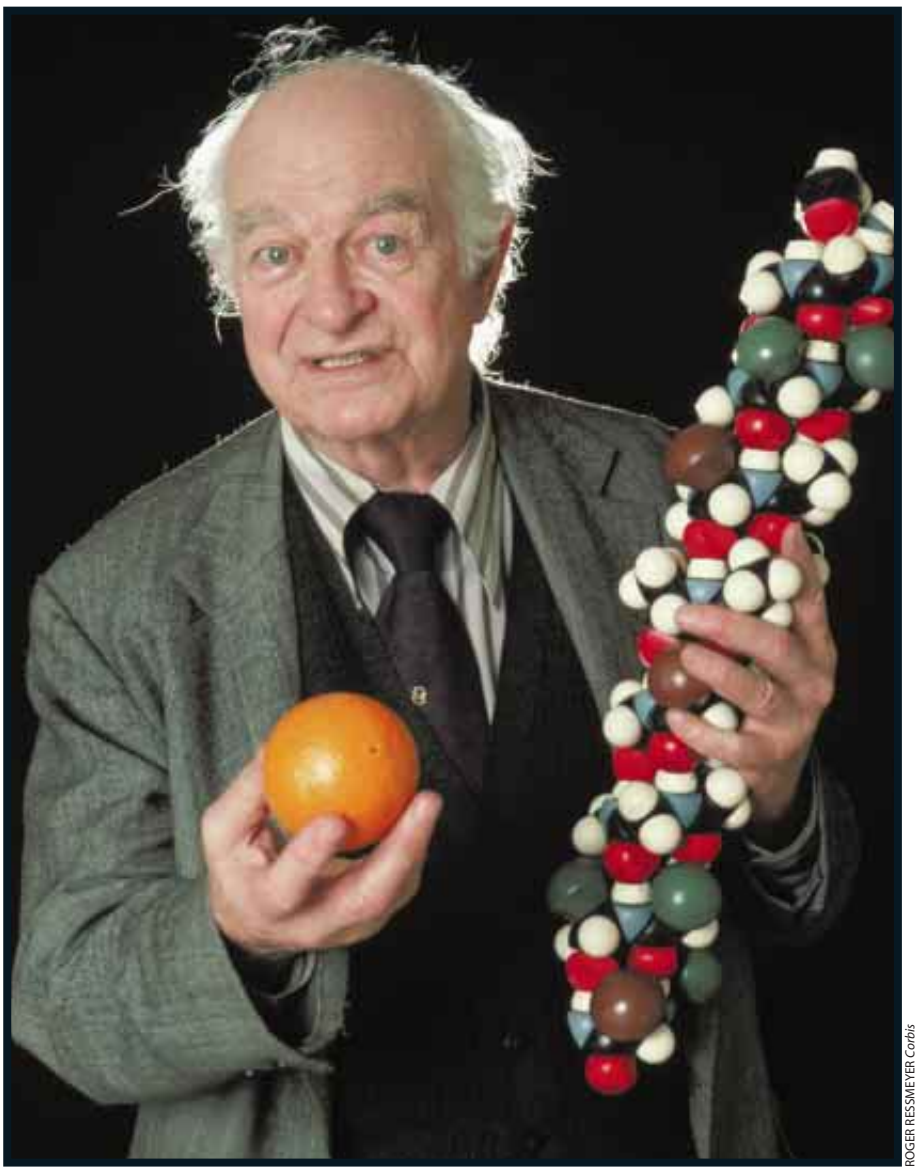
By the same logic, a vigorous exercise program would be good, too. But it can have some real drawbacks for those who revel in their laziness. Let's say, as some gerontologists believe, that a person who starts a program of vigorous aerobic exercise at the age of 40—three times a week for half an hour at a time—will live two years longer than she might have if she had remained sedentary. Those extra two years are just about the exact amount of time she spent exercising—not worth it, ultimately, for someone who hates jogging so much that she'd rather die a little sooner so that she can live a little happier.

Methuselah and Beta-carotene

What if there were some easier way toward a longer life, something that did not involve prolonged sacrifice? What if longevity could be packed into a pill? That is the Holy Grail that has driven hucksters and con men for centuries [*see box on page 36*], and it is the goal of many reputable researchers today. We have always looked for the easy way out; when studies showed that the healthiest people were those who ate the most fruits and vegetables, American industry promptly packaged the active ingredients into a more palatable form, the beta-carotene pill. This proved to be of little health benefit, though; whatever it was about fruits and vegetables that was keeping people healthy was probably not beta-carotene at all, or at least not beta-carotene without the other components of the plant itself.

As distinct from the snake-oil salesmen of old, today's life extensionists base their efforts on solid-sounding theory. They promote "antioxidant" compounds because of the "free radical theory of aging," which states that aging is a matter of cellular oxidation and can be slowed if you can prevent that oxidation. Or they look to hormonal replacement in anticipation that getting certain hormones back to youthful levels will lead to youthful functioning. But it remains to be seen whether any of these supplements or hormones really make any difference, either in prolonging life or in delaying the disabilities of age. So far whenever a "Methuselah factor" pill has sounded too good to be true, it turned out that it was.

Antioxidants, for instance, started out full of promise for their antiaging powers, but they still have not proved themselves in careful clinical trials. The most familiar antioxidants are vitamins A, C and E—especially vitamin C, which the brilliant chemist Linus Pauling celebrated in the final decades of his life. (Pauling lived to the ripe old age of 93, attributing his relatively good health to the megadoses of vitamin C he ingested every day.) Their action is thought to relate to what may be a basic underlying mechanism of aging: the buildup in the cell of molecules known as free radicals. Free radicals, the inevitable byproduct of cell metabolism, are highly reactive molecules that attach to and re-



ROGER RESSMEYER *Corbis*

MEGADOSE OF HYPE: Nobelist Linus Pauling linked high levels of vitamin C to prevention of cancer and heart disease, a claim that has never been substantiated.

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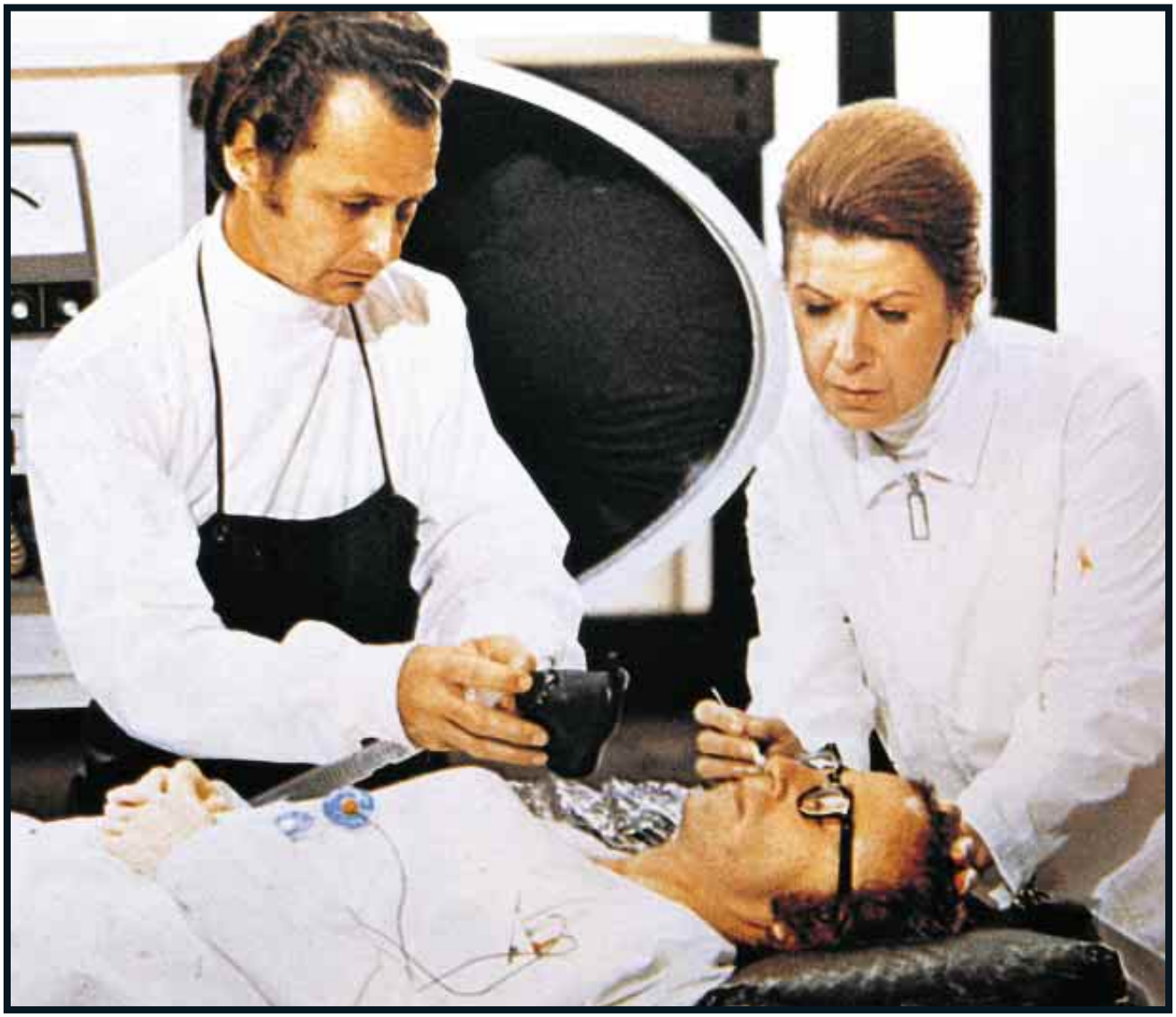

EVERETT COLLECTION

THE JOYS OF DEEP FAT: Woody Allen as Miles Monroe in the 1973 movie *Sleeper* is revived in the 22nd century into a world that has discovered that "life-preserving foods" include steak, cream pies and deep fat, not the wheat germ and organic honey sold in his health food store 200 years earlier.

act with structures in the cell and damage them. As more and more of these radicals accumulate, cell functioning gradually slows down [see "A Radical Proposal," on page 38].

Antioxidants reduce the chances that a free radical will turn into an oxidizing menace. The theory is provocative, but it has yet to be converted into any kind of substantive antiaging regime. In fact, studies involving beta-carotene have shown that this powerful antioxidant not only fails to slow aging or increase longevity but can even be bad for your health. One study designed to examine beta-carotene's protective effect against lung cancer actually uncovered a higher rate of lung cancer among male smokers who took beta-carotene than among comparable smokers who took a placebo. Another found that vitamin E provided no more protection against heart attack or stroke in high-risk patients than did either a placebo or a popular medication for blood pressure.

One new drug promoted for its antioxidant effect—and for its role as one of the body's most powerful internal clocks—is melatonin. The main function of this hormone, which is secreted by the pineal gland located in the center of the brain, is to help us differentiate night from day.

For this reason, it is not surprising that melatonin has proved to be useful for treating insomnia and jet lag. But claims have gone far beyond its effects on biorhythms. Melatonin is being promoted these days to prevent diabetes, cataracts, cancer, Alzheimer's disease, schizophrenia and epilepsy. It has also been said to extend life span (up to 20 percent, based on studies on laboratory rodents), treat depression, prevent sunburn and, of

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course, revivify an uninspired sex life.

Any single compound that is supposed to do all these things should raise a few eyebrows. It may turn out that melatonin does have some beneficial age-retarding and possibly even life-extending effect, but no one has proved this yet. We would be well advised to wait for some rigorously conducted studies before putting too much faith in this hormone, now sold over the counter in grocery and health food stores as a "natural" dietary supplement.

Other chemicals in the body are, like melatonin, present at significantly lower levels in old people than in young ones. Applying the logic that putting back what has been lost must be rejuvenating, people have been pushing supplements of "antiaging hormones" like DHEA, human growth hormone, estrogen and testosterone as the newest and most scientific-sounding form of youth-restoring nostrums.

GASLIGHT ADVERTISING ARCHIVES

Enter your health food store with extreme caution.

But any one of these in too large a dose can be dangerous. DHEA, for instance, has been associated with increased risks of breast and prostate cancers, liver problems, and masculinizing effects in women (acne, facial hair, voice changes and a more dangerous profile of blood lipids). For now, the jury is still out as to whether restoring hormones to a more youthful level bears any relation at all to making an older body look, feel or act like a younger one.

Perils of Wheat Germ

The message here is that you should enter your local health food store with extreme caution. From vitamin E to DHEA, the fickle wisdom of nutrition lore seems to mutate ceaselessly. In his 1973 movie *Sleeper,* Woody Allen spoofed the absurdity of the eternal quest for dietary elixirs. A scientist in the film, which takes place in the latter part of the 22nd century, talks of the health foods of the day—steak and cream pies—while expressing astonishment that denizens of the late 20th century consumed such unwholesome fare as wheat germ and organic honey.

The only intervention ever shown to extend maximum life span reliably, at least in laboratory animals, is calorie restriction—a strict dietary regimen also known as "undernutrition without malnutrition." Scientists have used this method to extend significantly the life spans of experimental rodents, insects and fish. In mice, for instance, limiting food intake to one-third fewer calories than normal increased a mouse's maximum expected life span of 39 months by more than 40 percent. This would translate in humans to a maximum life span of nearly 170 years [see "The Famine of Youth," on page 44].

Not only do calorie-restricted animals tend to live longer, but they tend to look and act younger every step of the way. They are leaner and more active than their fully fed agemates; their fur loses its pigment more slowly; they are less likely to develop cancer and other diseases of old age. Even at the age of two and a half—advanced old age for lab rodents—calorie-restricted mice tend to look young.

The question now is whether this approach will work in primates, including humans. Early results in monkeys appear promising. In the late 1980s gerontologists began calorie-restriction studies on 200 rhesus and squirrel monkeys; preliminary results indicate that with a 30 percent caloric restriction—once again, in a diet that emphasizes undernutrition without malnutrition—monkeys age more slowly and possibly live longer. The calorie-restricted monkeys have measurements of lean body mass, fat, blood pressure, triglycerides and insulin that are typically associated with their younger brethren. And their levels of the hormone DHEA decrease more slowly than expected.

But even if these monkeys live way beyond their normal life spans—and we will not know if they do for another decade or so—it is unclear that this can be translated into a benefit for humans. And without such assurance, who would willingly put himself on a diet of 1,500 calories a day? One of the few who has done so is Roy L. Walford, a respected gerontologist at the University of California at Los Angeles, who for the past 13 years has been limiting his food intake to about one third less than the rest of us.

In 1991 Walford signed on to the highly publicized "experiment" known as Biosphere 2. As the official team doctor, he expected that he would be called on to take care of injuries and infections for the other seven "biospherians" who lived together for two years in a self-sustaining greenhouse in the Arizona desert. But he ended up doing something quite different. Because of problems in the climate and agricultural parts of the experiment, food was scarce in Biosphere 2, and team members were restricted to about 1,500 calories a day, made up primarily of vegetables, beans, grains and fruit (mostly bananas). This was, in essence, the same calorie-restricted diet Walford had been following for four years. And here he was able to measure the effect of such a

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fountains of youth

In the summer of 1889 the highly respected Parisian neurologist Charles-Édouard Brown-Séquard made a stunning announcement to the Societé de Biologie. At the age of 72, he had concocted an emulsion drawn from the testicles of dogs and guinea pigs and had injected himself with it. He said he felt great—and he lived on, still feeling great, for another five years.

With Brown-Séquard's self-experiment, claims for "organotherapy" took off, and the testes of all kinds of animals—as well as their prostates, ovaries, pancreases, thyroids and spleens—were cut out and ground up for the sake of rejuvenating a gullible public.

EAST PHOTO/ROMPRES

RICH, RED QUACK: Ana Aslan became one of the richest women in Communist Romania during the 1970s by selling Gerovital, a tonic that turned out to be nothing more than ordinary Novocain.

But that 19th-century craze was only the most scientific-sounding approach in the quest for long life that dates back to ancient Greece and Rome, when the practice of "gerokomy"—the injunction for old men to sleep beside young virgins to regain their youthful vigor—was widely and quite enthusiastically entertained. Proof of the value of such a remedy was said to be long-lived Hermippus, headmaster of a Roman school for girls who supposedly lived to the age of 150. The reason? A lifetime spent breathing in the air around all those maidens.

Soon special potions were developed that also promised a longer and more fruitful life. During the Tang dynasty in seventh-century China, for instance, a "golden elixir" that took nine months to prepare was said to guarantee immortality. It was made mostly of cinnabar, combined with the red sulfate of mercury, a red salt of arsenic, potassium and mother-of-pearl. When you drank it, the story went, you turned into a crane, took up residence with the gods and lived forever.

In our own century, there have been dozens of treatments that were supposed to make you live forever. Yogurt was one. Remember the village of centenarians in the Caucasus Mountains of Georgia, the ones who appeared on the Dannon commercials with their ancient craggy faces, faded babushkas and cartons of supermarket yogurt? It turned out that not only was the theory of yogurt as an antiaging food—propounded by Nobel Prize–winner Elie Metchnikoff in the early 1900s—based on the mistaken assumption that aging was caused by intestinal toxins, but the villagers weren't nearly as old as they claimed. They just looked it.

Then there were restorative sea algae; the dried cells of fetal pigs, sheep or rabbits; and Gerovital. This last concoction was promoted in the 1970s by Romanian physician Ana Aslan. Aslan herself always looked younger than her age, and when she died in 1988 she had reached the respectable age of 91. Her spas and research institute had made her into one of the richest women in Romania, all from the sales of Gerovital—which turned out to be nothing more than simple Novocain, the painkiller you get in the dentist's office.

And how about amino guanidine? The drug attracted some attention in the mid-1990s for its ability to clear out the bulky sugar-protein molecules called AGEs, which were thought to age cells in the same way that oxidized free radicals do—by clogging cells and preventing them from doing their work.

Amino guanidine seems to have fallen off the antiaging radar, much the way that deprenyl, bioflavinoids and centrophenoxene have done. But never fear. New variations on old-fashioned snake oil—most of them dressed up in long scientific names ending in "ine" and "oid"—continue to gush through the pipeline. And, of course, they will keep on coming as long as people continue to look for the latest shortcut to the ever elusive fountain of youth.

—R.M.H.

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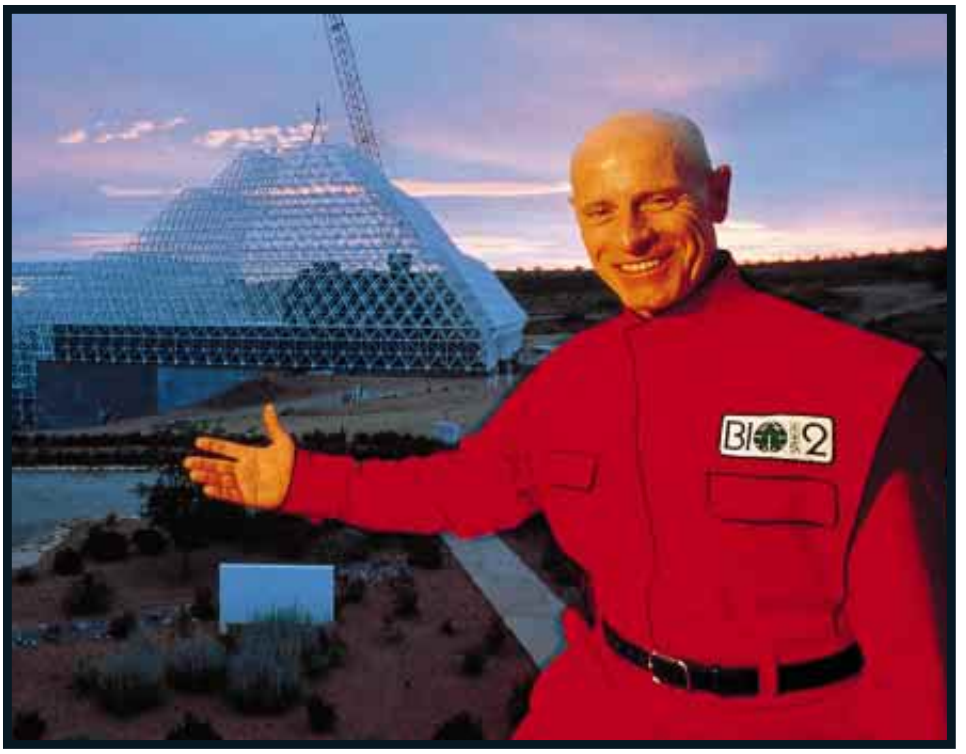

VOULGAROPOULOS *Liaison Agency*

DIETARY GUINEA PIG: Gerontologist Roy L. Walford was both participant and observer in an informal experiment in calorie restriction—the most promising antiaging approach—during the two years he spent in the self-sustaining Biosphere 2 greenhouse located in the Arizona desert (*seen in background*).

diet on the physiological changes of seven young people over the course of two years in their confined home.

"It happened just by a freak of chance that I should be positioned inside, taking care of these people, when the same kind of diet was forced on them," Walford has said. "So this, then, was an experiment of nature." His findings were that many of the physiological measurements that get worse with age—such as cholesterol, blood pressure and glucose metabolism—improved among the calorie-restricted biospherians.

Even if a calorie-restricted diet does ultimately add years to your life, is it worth sticking to, given the fact that it doubtless subtracts life from your years? Is it worth it to you to spend most of your life being vaguely hungry to gain another 10, 20 or 30 years?

Eating less to live longer may not be the only strategy to deal with the perils of aging. A significant stride toward renewal of fading flesh and organs may come from a small section at the end of chromosomes that seems to resemble an internal hourglass, counting off the number of times a cell divides until it reaches a kind of molecular old age and the relentless divisions halt. The telomere is a region at each end of the chromosome that acts like an aglet, the little hard tip at the end of a shoelace. Just as the aglet keeps the shoelace from fraying, the telomere keeps the chromosome intact. But it gets progressively shorter with each cell division, until it ultimately all but disappears. When that happens, the cell stops dividing—unless it is a cancer cell, which divides and grows in a way that becomes completely out of control [see "Counting the Lives of a Cell," on page 50].

Recently scientists have rejuvenated old cells by inserting the gene for telomerase, an enzyme that maintains the length of telomeres, and thus preventing the aglets from wearing away. In the laboratory, cells approaching the end of their natural lifetimes, a milestone called the Hayflick limit, begin dividing again, in some cases continuing to multiply indefinitely. Scientists still have no idea whether any of these cellular changes will ultimately translate into a longer life span for humans, but some researchers are optimistic that manipulating telomeres may serve as a treatment for reviving tired tissue.

It might sound like a dream come true—a world where nobody ages and where people live for 200 years or more—but such a world is still a long way away. This is a good thing, basically, because it gives us time to think about whether this is really a world we want to live in or whether there's something useful, in terms of maintaining the social balance to which we've become accustomed, in replacing the older generation at least every 100 years or so. In the meantime, each of us can do a tiny bit of "life extension" for ourselves if we so desire. If you set your alarm clock half an hour earlier every morning, you'll be awake for that much longer each day. At the end of 60 years, you'll have gained a year and a quarter of extra conscious moments during which you would otherwise have been asleep—about as many months as would be added to the average life span if we eliminated stroke as a cause of death. That is one way, only partly facetious, to obtain the grail of all these other longevity quests: to make you feel as if you've lived each day allotted you, however many that might be, to its absolute maximum.

Robin Marantz Henig *is author most recently of* The Monk in the Garden: The Lost and Found Genius of Gregor Mendel, the Father of Genetics.

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THERE MAY BE A WAY TO PREVENT OURSELVES FROM RUSTING FROM THE INSIDE OUT

a radical proposal

BY KATHRYN BROWN

WIZARD OF O_2: Water killed the wicked witch in Oz, but oxygen may kill us, oxidizing our cells the way it rusted Dorothy's pal the Tin Man.

You can drop cigarettes. Avoid alcohol. But there's one toxin you just can't dodge: oxygen. With every gulp of air, oxygen gives you life. Some of it, however, gets converted inside your cells into a radical molecule that can wreak havoc, degrading those same cells and others. A growing number of scientists say this damage is what causes aging. They also think they may one day be able to fend off oxygen's ill effects and help us live a lot longer.

Scientists have long known that oxygen is capricious. As molecules go, it gets around, reacting with all kinds of things. Mostly, that's good. Oxygen combines with fats and carbohydrates, in a part of cells known as the mitochondrion, to churn out the energy that gets you through the day. But the conversion isn't perfect. A small amount of oxygen is regenerated in a nasty form called a free radical, or oxidant—the very critter that causes metal to rust. The oxidants careen about, binding to and disrupting the membranes, proteins, DNA and other cell structures that make your body work. Over time, this damage adds up, and the result just might be an older, frailer you.

According to one estimate, oxidants bombard the DNA inside every one of our cells roughly 10,000 times a day. Thankfully, most of the assailants are intercepted by a small army of antioxidant chemicals. Proteins also patch up the damage caused by the radicals that do get through. "The house is always getting dirty, and we're always trying to clean it up," remarks John Carney, chief technical officer at Centaur Pharmaceuticals in Sunnyvale, Calif., which is developing drugs to fight various diseases of aging. But eventually, the theory goes, our tired cells get less efficient at repelling free radicals and mopping up oxidative messes, and the damage accumulates. We begin to rust from the inside out.

If oxidants do send us crumbling into old age, then ramping up our biochemical defenses should extend life. That's what scientists are finding, at least in the flies, rats, worms and other animals they have under scrutiny in the laboratory. Whether the techniques they are pursuing will ever lengthen life in humans remains an open question. But some researchers think they're getting close to an answer. "The key is to really understand how oxidative damage works, and we're learning that," says biochemist Bruce N. Ames of the University of California at Berkeley. "I'm convinced life expectancy will get longer a lot faster than anybody thinks."

The Original Pollutant

Oxygen's checkered past goes way back—about two billion years. Around that time, scientists believe, cyanobacteria began releasing more and more oxygen into the earth's atmosphere, until many organisms were forced to either accommodate the gas or risk being degraded by its corrosive nature. Over time, some particularly oxygen-adept bacteria evolved into mitochondria, the tiny powerhouses in all human cells that use oxygen to help turn food into energy.

The "free radical theory of aging" was first laid out

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about 45 years ago by Denham Harman of the University of Nebraska. The idea won credibility in 1969, when scientists identified a key antioxidant, superoxide dismutase (SOD), an enzyme that breaks down the harmful superoxide, a leader among the various free radicals that can form inside the human body. Soon researchers began to realize that mitochondria created oxidants in high amounts. And by now dozens of experiments have linked oxidative damage and aging.

Until recently, however, that link had been a matter of indirect correlation. In the lab, for instance, some young human cells do far better than older cells at resisting or repairing oxidative damage, whether the cells are being doused with hydrogen peroxide or stuck inside a chamber filled with pure oxygen. Also, lab flies, worms and mice carrying genetic mutations that proffer long life tend to withstand oxidative assaults better than their peers. "All these studies suggest oxidative damage may be an important part of aging, but they lack the kind of direct experiments to nail that link down," notes John Tower, a molecular biologist at the University of Southern California. "The question is, if we actually alter oxidative stress, will it extend life?"

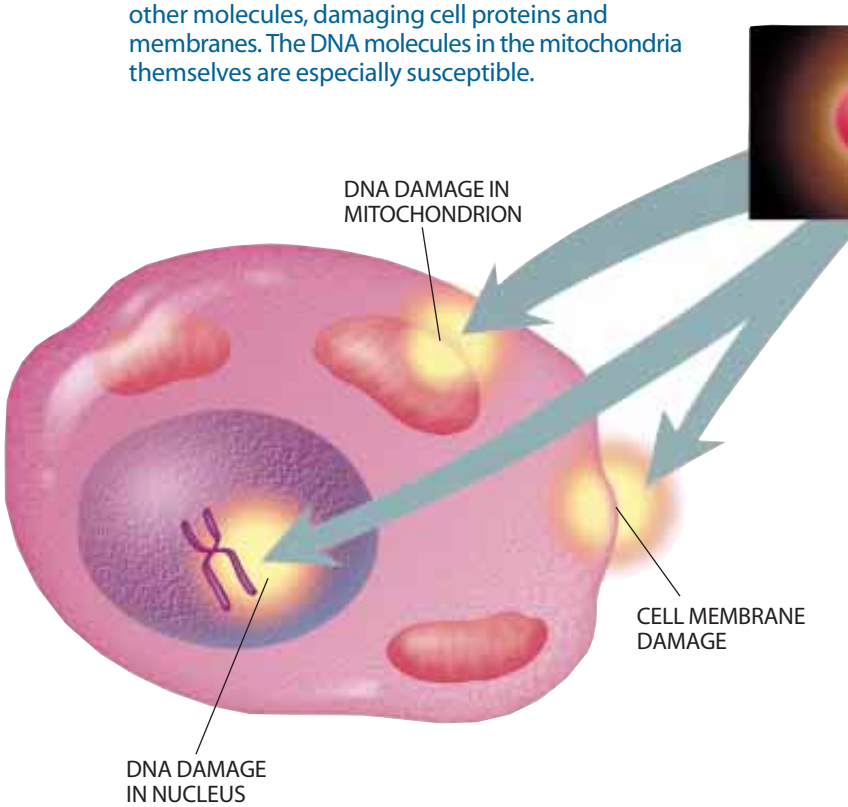
To find out, Tower and his U.S.C. colleague Jingtao Sun recently reared fruit flies with an engineered protein that could—when exposed to heat—turn up the activity of SOD and another antioxidant, catalase. The flies started life in the lab normally, along with a control group of flies. Then, on the fifth day, the experimental flies got pulses of heat, ratcheting up their antioxidant defenses. The results were striking. Most of the everyday flies keeled over long before six weeks—but those with supercharged SOD, in particular, survived an average of 48 percent longer. "That's pretty convincing evidence that overexpression of SOD extends life," Tower says.

That's not the only evidence. Five years ago William Orr and Rajindar Sohal of Southern Methodist University in Dallas equipped their own flies with extra copies of genes for SOD and catalase. Those flies lingered up to a third longer than their normal maximum life span—and seemed to age more slowly along

cellular damage and defense

In cell metabolism, the mitochondria convert glucose and oxygen into energy. Oxygen radicals also form as a normal by-product.

The highly reactive oxygen radical can bind with other molecules, damaging cell proteins and membranes. The DNA molecules in the mitochondria themselves are especially susceptible.



JOHN W. KARAPELOU

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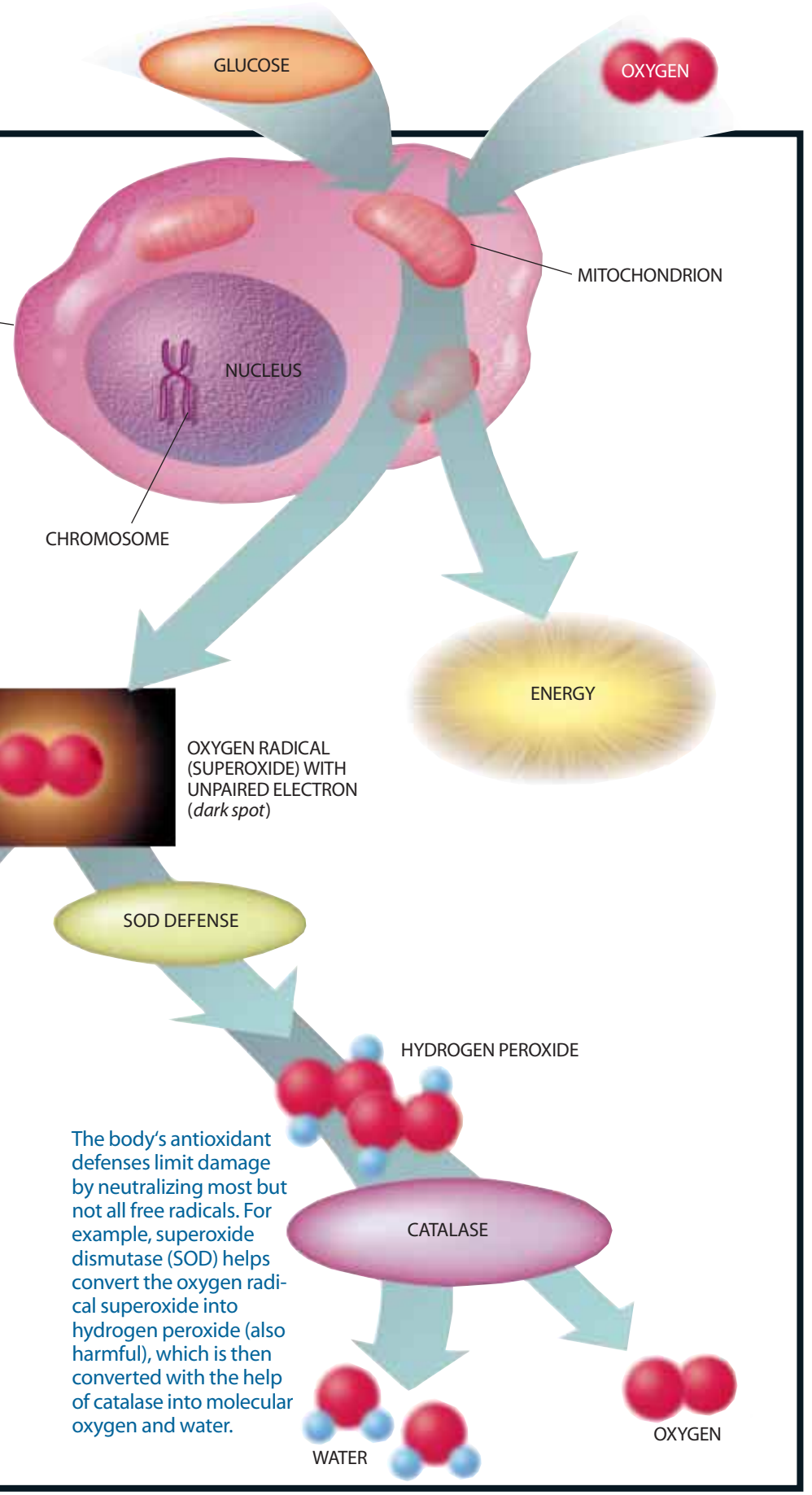

The body's antioxidant defenses limit damage by neutralizing most but not all free radicals. For example, superoxide dismutase (SOD) helps convert the oxygen radical superoxide into hydrogen peroxide (also harmful), which is then converted with the help of catalase into molecular oxygen and water.

the way, exhibiting higher energy, faster movements and less oxidative damage. Eventually, Sohal says, similar studies will be done with mammals and then, if deemed safe and efficient, with humans.

Intercepting the Interloper

In the meantime, scientists hope to pinpoint exactly where oxidants do their dirtiest work—and ways to intervene. The idea, says molecular biologist John Phillips of the University of Guelph in Ontario, is to tailor therapies to the most important injured cells, rather than trying to fight oxidative damage throughout the body. Phillips has one candidate cell in mind: the motor neuron, which directs muscles from the brain and spinal cord. People with a paralyzing disease called familial amyotrophic lateral sclerosis die early, with heavily damaged motor neurons as well as mutations in SOD. Maybe motor neurons are a critical target of oxidants, kick-starting or dominating the process of aging.

To test that idea, Phillips and his coworkers bred fruit flies with a jolt of one of the human superoxide dismutase compounds, SOD1, to be expressed only in the flies' motor neurons. Sure enough, the bugs lived 40 percent longer than normal. And those extra days were lively ones. "We didn't just delay dying, so that we had geriatric flies living longer," Phillips says. "The extended time of life was youth." In contrast, boosting SOD1 levels in unrelated muscle cells seems to have had no effect on the flies' life span, he adds. Still, questions remain. "We don't really know why these animals are living longer," Phillips concedes. To pin down SOD's relevance, the team is now spiking different types of neurons with the antioxidant to see how the various cells react.

Another target for protection is the mitochondria inside all cells. Because these tiny powerhouses are the very source of harmful oxidants, they're the first cell structures to be clobbered by the chemicals. In a 1998 study Sohal and his co-worker Liang-Jun Yan exposed flies to high doses of pure oxygen and then went looking for signs of oxidants at work in the flies' mitochondrial membranes. Rather than far-flung havoc, they

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found that oxidants targeted several vulnerable proteins, attaching to their strings of DNA, forcing them out of work and upsetting the entire cell's ability to act normally. "Free radical damage during aging is not random, causing decline all around our cells," Sohal says. "We're talking about damage that's very selective, and that may mean aging comes from specific biochemical losses."

Proof of this notion would be good news, Ames says. "The key thing is to understand how aging really works. If it's the decay of mitochondrial DNA, well, we can do things to beef up these old mitochondria."

Ames, Tory Hagen of Oregon State University and their colleagues have done just that. In preliminary work, they found that the liver cells of older rats do not fend off free radicals as well as the liver cells of younger rats do. So last year, over a two-week period, they fed a group of older rats food laced with lipoic acid, a chemical that the mitochondria can convert into a potent antioxidant. After this high-powered diet, the older rats' liver cells deflected oxidant intruders with greater resilience. What's more, the senior rats scrambled around with new spirit and a sleeker look. "I don't want to say we've gone so far as turning old rats back into young rats," Ames says, "but that sure looks like what's going on in the mitochondria." The team has just begun a study to see whether the antioxidant-endowed rats actually outlive their lab mates.

Supermarket Solutions

If antioxidants work for flies and rats, what about us? Can you down a daily supplement that will extend your years? Don't count on it. "Everybody is talking about popping antioxidant vitamins," Phillips groans. "The evidence is strong that taking moderate amounts of vitamin C and E is not harmful, but the evidence that it's actually useful for delaying aging is very thin." For one thing, researchers say, your body can absorb only so much of these vitamins; the rest goes the way of other wastes. Also, in the industrial world, most of us get enough of the basic antioxidants in our daily diets. In contrast, lab animals that live unusually long with extra antioxidants may be deficient in those chemicals to begin with.

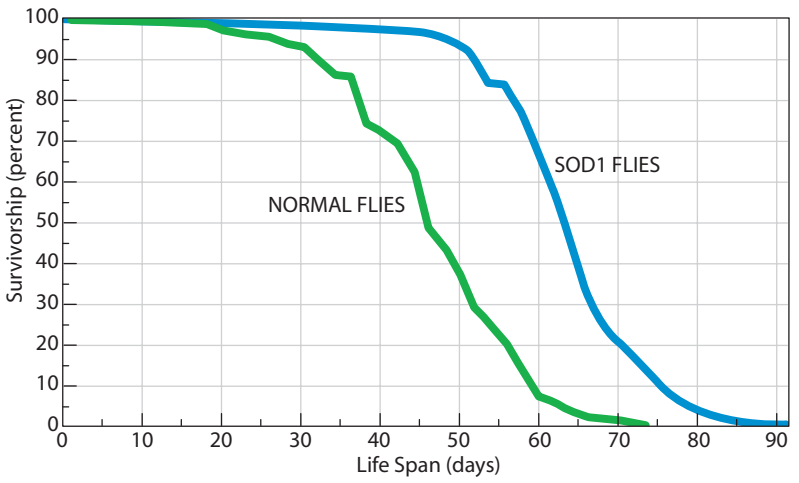
Even if antioxidant supplements do boost your defenses against free radicals, it's tricky to know which ones—or how much—to take. As with any ingredient, too much can be a bad thing. In 1996, for instance, two large studies made news when researchers discovered that beta-carotene supplements—thought to help ward off some types of cancer—actually increased rates of lung cancer among smokers who were taking the pills. Some antioxidants hawked in health food stores will never do any good; walk right past those bottles of SOD, catalase and glutathione peroxidase, because these compounds must be created inside the body. When swallowed, they are simply broken down in digestion and rendered useless, researchers state.

Still, there are some antioxidants that hold promise, Ames says, such as lipoic acid, which directly protects the mitochondria. Perhaps, he adds, some of the more obscure antioxidants dry up in the body as we age, leaving us more vulnerable to oxidative damage. If that's the case, downing extra amounts of these conditional nutrients might slow aging's cellular effects. "We just don't know yet," Ames says.

Indeed, there are a lot of unknowns. What proportion of aging changes in cells are the result of oxidative damage? Is there a way to reduce the rate of oxidants the body churns out, rather than simply boosting antioxidants? And what do all these long-lived lab mutants really explain about oxidative stress in people? Sohal worries that some of the most touted studies are misleading. For instance, biologists have won lots of attention by reporting that in worms, single mutations in a gene called *daf-2* can double life span, partly by resisting oxidative stress. But this is a "bogus kind of life extension," charges Sohal, because the worms' metabolism (energy level) plummets during their extra time on earth. "It's just like going to sleep for three years and calling those three extra years of life," he says. The extra time is akin to hibernation, Sohal adds, so any therapy based on it would rob people of the energy they normally have.

The most basic challenge is understanding aging itself. Growing old is a slow, subtle process that's hard to de-

rust inhibition: an enzyme extends life



LONGER YOUTH: Fruit flies bred with a dose of SOD1, an antioxidant enzyme that breaks down free radicals, lived 40 percent longer than normal fruit flies did in a University of Guelph laboratory. Notably, the phase of life extended was youth, not old age.

LAURIE GRACE; SOURCE: JOHN PHILLIPS *University of Guelph*

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fine with blood tests or cellular studies. Oxidants can muddy the picture, observes Carney of Centaur Pharmaceuticals. After all, these omnipresent molecules can strike a cell's proteins, fats or DNA, all very different beasts. "Understanding oxidative damage and the biology of aging is a massive undertaking," he points out.

In the short run, Carney says, researchers may first unravel the role of oxidants in specific diseases of aging. Centaur, for instance, is working on drugs to fight Alzheimer's and Parkinson's diseases. People who suffer from these conditions show telltale signs of oxidative damage in the brain. Eventually these studies may inch scientists closer to understanding basic brain changes during aging. Carney has reason to be optimistic. Some 10 years ago, while at the University of Kentucky, he and his colleagues were the first to report that high levels of a synthetic antioxidant, PBN, can decrease harmful oxidative proteins in the brains of old gerbils. "Aging may indeed be a treatable process," Carney maintains.

Self-Imposed Treatment

Some individuals are prescribing their own treatments. According to one idea, you can starve yourself, cutting back on calories until your metabolism drops so low that fewer free radicals are formed in the first place. A more pleasant alternative, perhaps, is munching on fruits and vegetables that are high in antioxidants. Last year neuroscientist James A. Joseph of Tufts University and his colleagues reported that middle-aged rats fed extracts of spinach, blueberries or strawberries for eight weeks showed marked declines in oxidative stress in their brain cells, as well as improved memory and coordination. The most successful rats noshed on blueberries—the equivalent of a cup a day for humans.

The research also highlights how much scientists have to learn about the processes that contribute to aging. Apparently, it's the blend of ingredients inside blueberries—not just isolated antioxidants—that benefited the racy rats. Studying the rats' brain cells, Joseph was surprised to find relatively few signs of increased antioxidants. Instead he found a host of cell changes, from better anti-inflammatory activity to more pliable membranes—all of which could act together to combat aging changes.

"If you take a supplement, you never get the benefit of a fruit or vegetable that contains hundreds of compounds," Joseph says. Right now researchers can't even identify all the compounds, much less explain how they might work together to fight free radicals. The answers could be years in coming. In the meantime, he asks, why not stroll down the produce aisle? A few berries might just offset a little oxidation—or at least make the wait for answers to aging that much sweeter.

the antioxidant diet

Your best bet for fending off cellular damage from free radicals, scientists say, is to maintain a healthy supply of antioxidant compounds by eating fruits and vegetables—not by taking a pill. Here are some foods rich in antioxidants.

Fruits: blueberries, cherries, kiwis, pink grapefruit, oranges, plums, prunes, raisins, raspberries, red grapes, strawberries

Vegetables: alfalfa sprouts, beets, broccoli flowers, Brussels sprouts, corn, eggplant, kale, onions, red bell peppers, spinach

KEVIN R. MORRIS *Corbis;* SOURCE: U.S. AGRICULTURAL RESEARCH SERVICE

Kathryn Brown *is a writer at* Science News *in Washington, D.C.*

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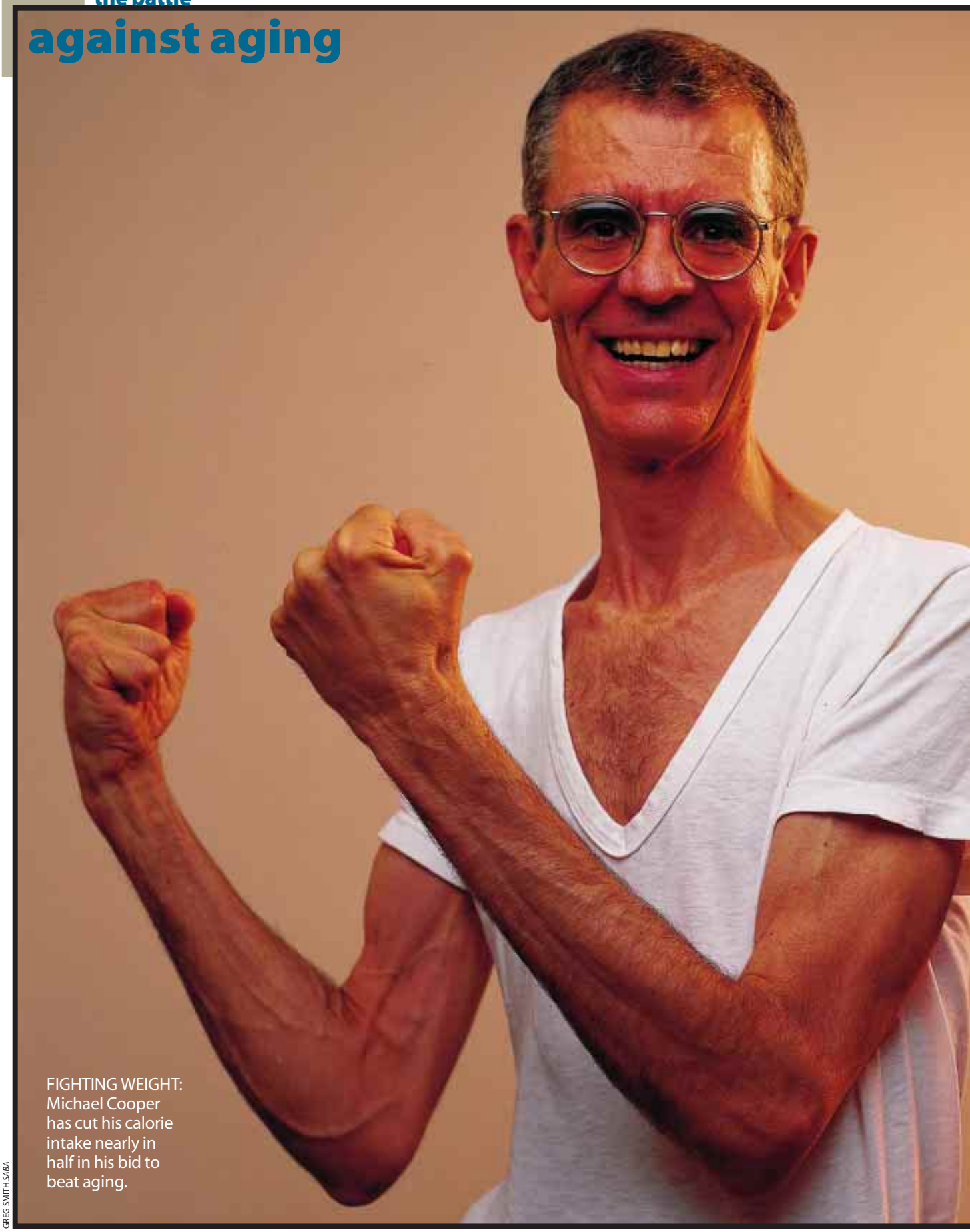

FIGHTING WEIGHT: Michael Cooper has cut his calorie intake nearly in half in his bid to beat aging.

GREG SMITH *SABA*

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SEVERELY RESTRICTING DIET MAY INCREASE LIFE SPAN, BUT FEW WILL BE ABLE TO FOLLOW SUCH A HARSH REGIMEN

the famine of youth

BY GARY TAUBES

Despite the national propensity for fad diets and miracle health cures, despite the ubiquitous talk of "eating healthy"—a concept so mercurial that every decade brings a new definition—only a single dietary regime has ever been conclusively demonstrated to extend the life span and improve the health of laboratory animals, let alone humans. It is known in the scientific lingo as "caloric restriction" or "calorie restriction" and less technically as "eating considerably less than you might normally prefer"—perhaps 30 to even 50 percent less. In other words, an average-size human on a calorie-restricted diet might consume 1,500 calories a day, compared with the 2,100 calories of the typical American. It's four or five small meals a day, predominantly vegetables and fruits, and a life in which you are perpetually cold, painfully thin and constantly hungry. Calorie restriction, quite simply, is a Draconian diet and a lifelong one at that. "It requires a psychological profile only one person in 1,000 has," says Richard Miller, associate director for research at the University of Michigan Geriatrics Center.

Nevertheless, the study of calorie-restricted diets has lately become a hot-ticket item among longevity and nutrition researchers, who have taken to extolling its virtues with remarkably unrestrained enthusiasm. Their reasons are clear—the list of the beneficial effects of calorie restriction in laboratory animals reads like the packaging on a miracle cure. Calorie restriction will, for instance, increase both average and maximum life spans, and the fewer calories consumed, the greater the increase; it will reduce the occurrence of virtually all age-related diseases, including heart disease, diabetes and cancer. It will prevent kidney disease and cataracts as well as the development of Parkinson's and Alzheimer's diseases. It will lower blood cholesterol and forestall the age-related deterioration of the immune system. In mice, calorie restriction from an early age raises the maximum life span from 39 months to 56 months and at the same time preserves what passes for intellectual function: a three-year-old calorie-restricted mouse, for example, can negotiate a maze with the quickness and ease of a normally fed mouse of six months, which is the mouse version of salad days.

This harsh regime has been shown to work its life-extending magic on almost every species that's ever been tested—from paramecium and worms to spiders, insects, rodents and (although the data are still preliminary) primates. The two caveats are that the later in life the animals start on caloric restriction, the less the benefit, and that the diets must include plentiful amounts of vitamins and minerals. The an-

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imals must be undernourished without being malnourished, as calorie-restriction researchers say.

All of this, though, leaves researchers struggling to answer three key questions: What exactly does calorie restriction do physiologically to extend longevity and fight off disease? Will it have the same effect in humans? And, if so, is there a way to get the benefits without the actual diet? "The purpose of studying calorie restriction," Miller says, "is not to develop yet another diet that people won't follow." Rather researchers would ideally like to concoct a pill or potion that will mimic the effects of calorie restriction and produce the benefits while allowing us to eat to our heart's content.

In the 65 years since Clive M. McKay of Cornell University first noticed that the regimen doubled the life span of his lab rats, and in the decade or so since calorie restriction moved from the fringes of longevity research to the mainstream, much of the laboratory work has been aimed at discerning the fundamental biology underlying the beneficial effects. What researchers generally agree on is that the response to calorie restriction in organisms seems to be an evolutionary adaptation to periods of scarcity. As food becomes hard to find, organisms evolve ways to "up-regulate" those defense mechanisms that increase life span and down-regulate reproductive mechanisms. That would keep the organisms alive long enough to find food, and at that point they could go back to reproducing and to a normal aging process, which is exactly what happens in the laboratory.

The question of how this might work is still open. The leading hypothesis is that calorie restriction reduces the amount of oxidative damage to the body. Oxidative damage is the foremost theory as to what causes the deterioration that comes with age. The concept is known in the business as the "oxygen paradox": we require oxygen to turn the food we eat into cellular fuel, but the side effects of this oxygen metabolism are detrimental to our health. The process takes place in cellular factories called mitochondria, where electrons are stripped from energy-rich substances—in particular, glucose—while converting them to the kind of fuel that cells can use.

The electrons are then captured by oxygen atoms, which join with hydrogen to form water. But the process is inefficient, and the electrons often go astray, resulting in the formation of highly reactive molecules known as free radicals. Roy L. Walford, a gerontologist at the University of California at Los Angeles and a pioneer of calorie-restriction research, refers to free radicals as "great white sharks in the biochemical sea—short-lived but voracious agents [that] oxidize and damage tissues."

The oxidation that occurs in the human body is identical to the way in which rust is formed in metals, so it is not unreasonable to say that we will all eventually rust to death if given the opportunity. The free radicals damage the tissues but also seem to damage the genetic material, the DNA, that codes for the proteins required for the body's physiological functions. The primary candidate for most of this damage is the mitochondria themselves, which are not spared by the free radicals they produce. And once damaged, they produce even more free radicals.

Calorie restriction, by this theory, reduces the amount of fuel available for cells and the amount of oxygen needed by the mitochondria to convert the existing fuel into energy, and it makes the existing metabolic process more efficient. Not only do the mitochondria gen-

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erate fewer damaging free radicals, but the lack of food also seems to up-regulate the production of enzymes that neutralize the free radicals.

In one of the more fascinating experiments in the field, Richard Weindruch and Tomas A. Prolla of the University of Wisconsin–Madison recently compared the expression of genes in young mice, normally fed aging mice and calorie-restricted aging mice. Weindruch, who has been studying calorie restriction since he was a U.C.L.A. graduate student in the mid-1970s with Walford, believes that the process lowers oxidative stress and damage to the mitochondria while having its effect predominantly in "critical target tissues" such as the brain and nerve cells and heart and skeletal muscle. "All these tissues depend heavily on mitochondrial energy metabolism to generate cellular energy, and all these tissues have fairly limited repair capabilities," he says.

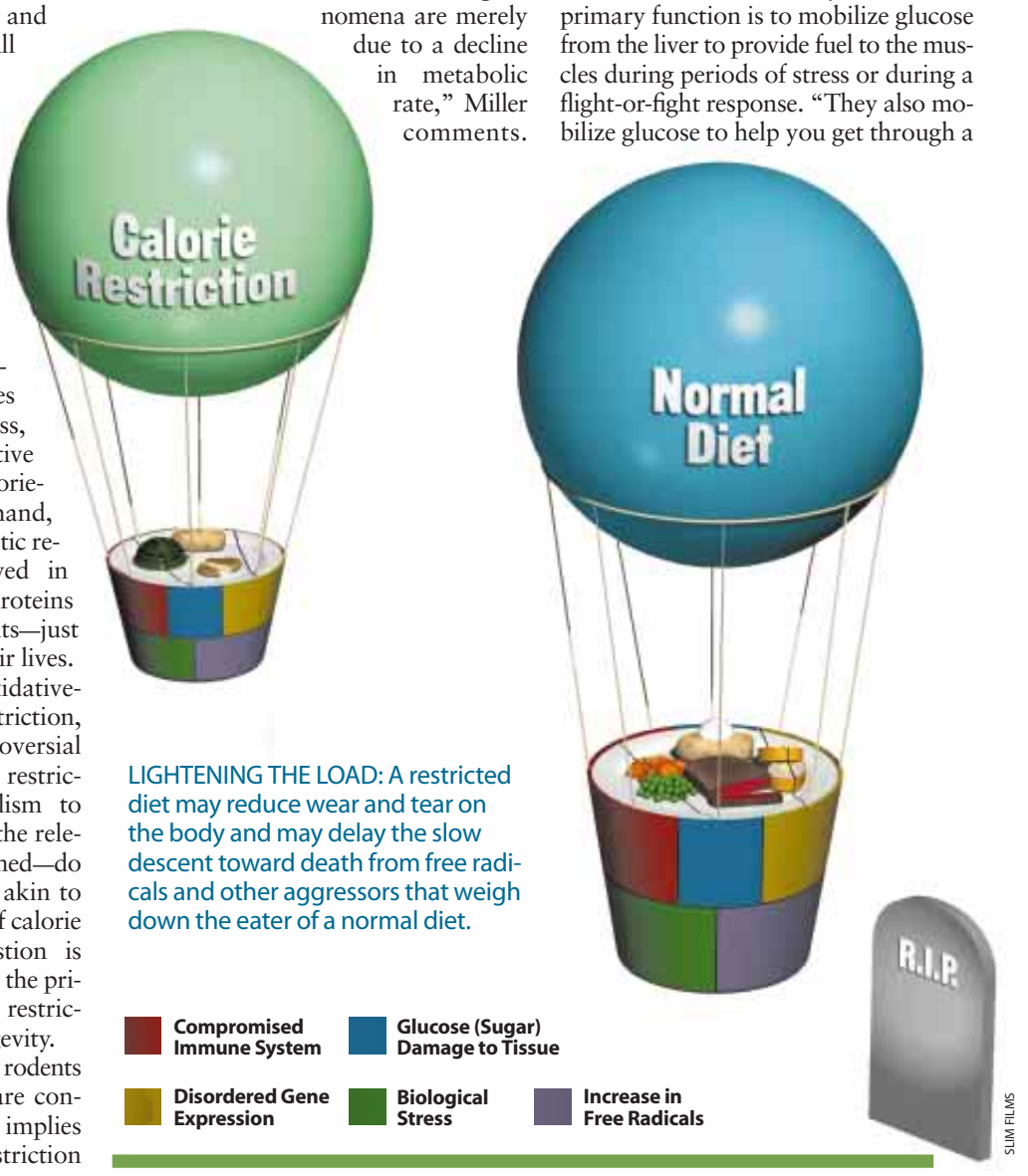
Weindruch and Prolla examined tissues from the calf muscles of mice and found that normally fed aging mice were putting most of their genetic effort into repairing genes and proteins damaged by stress, of which a good part is oxidative damage. The active genes of calorie-restricted mice, on the other hand, were much less involved in genetic repair and much more involved in biosynthesis—building new proteins and other cellular components—just like the mice in the prime of their lives.

Most researchers buy the oxidative-damage theory of calorie restriction, but they disagree on two controversial aspects. One is whether calorie restriction actually lowers metabolism to achieve its goal, in which case the relevance to humans might be lessened—do we have to go into something akin to hibernation to get the benefits of calorie restriction? The second question is whether lowering metabolism is the primary route that allows calorie restriction to achieve its effect on longevity.

The fact that calorie-restricted rodents have body temperatures that are considerably lower than normal implies that the benefits of calorie restriction come about because the less food eaten, the lower the metabolism and, hence, the lower the oxidative damage. "It's known that rodents can decrease their body temperature, their metabolic rate, and that [that] is how they survive famine periods," says Rajindar S. Sohal, a biologist at Southern Methodist University. "But mice and rats are not humans. We don't have that mechanism." Other researchers, however, disagree with this interpretation of the evidence, and the argument often comes down to a dispute about how best to measure metabolism in normally fed versus calorie-restricted animals. "It's a distinct oversimplification to say that the calorie-restriction phenomena are merely due to a decline in metabolic rate," Miller comments. "And many of the changes that occur in calorie-restricted rodents are hard to explain by the idea that fuel and oxygen consumption go down."

A Shot of Hormones

That there is more going on is suggested by the work of James F. Nelson, a physiologist at the University of Texas Health Science Center at San Antonio. Nelson and his colleagues have shown that calorie restriction subtly raises the levels of hormones called glucocorticoids. These hormones do "probably a zillion different things" in an organism, Nelson says, of which researchers have nailed down only a few. Their primary function is to mobilize glucose from the liver to provide fuel to the muscles during periods of stress or during a flight-or-fight response. "They also mobilize glucose to help you get through a



LIGHTENING THE LOAD: A restricted diet may reduce wear and tear on the body and may delay the slow descent toward death from free radicals and other aggressors that weigh down the eater of a normal diet.

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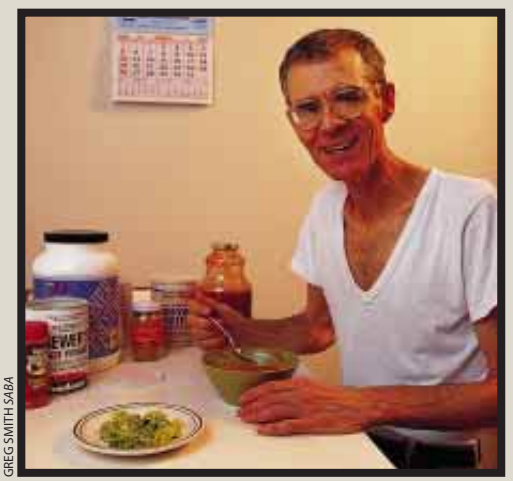
four square
snacks a day

Michael Cooper, suffice it to say, is obsessed with the problem of aging and has been since he was a boy. He recalls looking at his seventh-grade teacher, a balding man in his 50s, and thinking, "I don't want to be like him," and, he says, "Those thoughts never left my mind." Now Cooper is 51, a former electrical engineer who recently went back to school to study biology at Southern Methodist University. Since the mid-1970s he has been reading voraciously about longevity, nutrition and health. And in February 1986 he began practicing calorie restriction, hoping to extend his life well beyond the biblical three score and 10 years. The 6'2" Cooper has reduced his daily calorie intake from 2,800 to 1,500, and his weight has dropped over a seven-year period from 160 pounds to a feather-light 120.



GREG SMITH *SABA*

THE SKINNY ON AGING: Michael Cooper consumes a 350-calorie lunch that includes whey protein, brewer's yeast and broccoli.

Cooper would have gone lower, but he found plenty of reasons to convince him otherwise. "For one thing," he points out, "if I was any thinner I would probably freeze to death. I wear long thermal underwear year-round in Texas, and I can't generate any body heat. If I sit still, I get cold even in a warm room. I have a little bit of digestive trouble, probably related to consuming too few calories. And my bones are quite vulnerable. They're more sensitive to sitting. I have to sit on a pillow. And my feet don't have any pad on the bottom. So I have to extra-pad my shoes. It's not a big deal; I get along just fine."

As for his daily diet, he explains, it's basically the equivalent of a handful of snacks a day: "Most wouldn't consider it very tasteful, but I like it a lot. In the morning, for instance, I mix up wheat bran and solid protein, and I put some canned pumpkin in it, a little bit of spices and occasionally half a cup of yogurt. For lunch I have vegetables. For supper I have two meals, one at about 5:00, which is just vegetables, maybe three different kinds. And around 7:30 I have what I call dessert, which might be berries mixed up with whey protein."

So far Cooper sees little evidence that his severe diet has slowed the aging process, and it certainly hasn't diminished the unaesthetic side effects, although he remains relentlessly optimistic. "My hair is thinner," he notes, "and when you're thinner you look older. Wrinkles show up more. On the other hand, if I weren't doing this I might already be in decrepit condition. I have no way of knowing. And even if I come down with a disease like cancer or heart disease and I know I'm going to die, I figure I've probably gained a few years by doing what I've done." —*G.T.*

fasting stage, to keep blood sugar high enough so you can keep going to your next meal," he says. These hormones, too, serve to fight inflammation, hinting that they play a direct role in the survival of the organism. And glucocorticoids are only one of a host of hormones in laboratory animals that seem to be affected by calorie restriction.

The Human Question

Nelson and his colleagues are currently testing lab animals to find out if the hormonal changes in calorie-restricted animals are a side effect of calorie restriction or a mechanism that directly leads to longevity. In one experiment, for instance, Nelson's laboratory is spiking the drinking water of lab mice with glucocorticoids to determine if the mice live longer. "The next thing would be to see if any of these effects are translatable to humans," he asserts.

The human question is the big one. The existing data on humans are very thin. Most human populations that are forced to survive on low-calorie diets are also malnourished and are as likely as not to die prematurely from vitamin and mineral deficiencies. The only known exception is on the Japanese island of Okinawa, Walford notes: "The Okinawans have about 70 percent of the calorie intake of the rest of Japan. They eat mainly fish and vegetables. They have as much as 40 times the incidence of people over 100. They have less diabetes, tumors and so forth than the rest of Japan."

On the other hand, he adds, there could be numerous other factors that contribute to the Okinawans' longevity. Doing a controlled trial of calorie-restricted humans is impractical for what David B. Allison, an obesity researcher at St. Luke's-Roosevelt Hospital Center in New York City, calls "the obvious reasons": researchers would have to convince hundreds or thousands of humans to spend the better part of their lifetime living on an extreme diet, without being able to promise them benefits. And the trial would, by definition, take the better part of a century to complete.

Instead the National Institute on Aging (NIA), in collaboration with Wein-

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DAVE BARTRUFF *Corbis*

druch and his colleagues, is testing the calorie-restriction proposition on rhesus and squirrel monkeys, assuming that if it works for any primates, it's a good bet it would work for humans. They now have some 200 monkeys in the trial, half on a calorie-restricted diet and half eating normally. Even these monkeys are likely to live 30 or 40 years, so the study is a long-term endeavor. But the calorie-restricted monkeys are already showing signs of unnaturally robust health.

With so little information on whether calorie restriction will benefit humans, researchers have barely touched on how to mimic its effect without going on a diet that could take the fun out of living, and certainly out of eating, for almost anyone willing to try it. One possibility, Allison says, is to give all people, not just the excessively overweight, anti-obesity drugs. This would suppress appetite, but a healthy *un*satisfied appetite may be a necessary factor in convincing an organism that famine has arrived and thus stimulate the beneficial effects. "That this might lengthen life is real speculation, and it goes far beyond any data," Allison observes. "We've never demonstrated in humans that antiobesity drugs even make the obese live longer, let alone the average-weight person."

At the NIA, George S. Roth, Donald K. Ingram and Mark P. Mattson are trying another tack—fooling cells into thinking they've been fed when they haven't. They're using a compound called 2-deoxy-D-glucose, which is virtually identical to glucose but lacks two oxygen atoms. Once inside the body, it goes where glucose would normally go, but it can't be metabolized by the cells. The compound is synthetic, relatively inexpensive and has been used in research laboratories for years. It's also mildly toxic in high enough doses, however, which makes it a debatable intervention for humans even if it works.

UNCONTROLLED EXPERIMENT: Okinawans, with 70 percent of the calorie intake of other Japanese, count among their number up to 40 times as many centenarians as their countrymen do.

The researchers gave moderate doses to rats for six months—not long enough to establish whether the compound increased longevity but long enough to see if it might. With the 2-deoxy-D-glucose added to their diet, the rats continued to eat the same amount of calories, and yet they lost weight and their body temperature dropped, as it would have had they been dieting. Their insulin levels also dropped, another hallmark of calorie restriction. This convinced the NIA researchers that 2-deoxy-D-glucose was worth testing for the lifetime of the rats, a study that's ongoing. If the rats do indeed live longer, the NIA researchers will at least have proved that the mimetic phenomenon, as they call this calorie-restriction mimicry, has promise. "Then we'll look for other kinds of compounds that exert the same effects without any toxicity," Roth says. That would mark a big step toward the ultimate goal of letting people have their cake and live longer, too.

Gary Taubes *is a California-based science writer.*

Further Information

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Roy Walford, the gerontologist who is observing a calorically restricted diet, maintains a site at www.walford.com on the World Wide Web.

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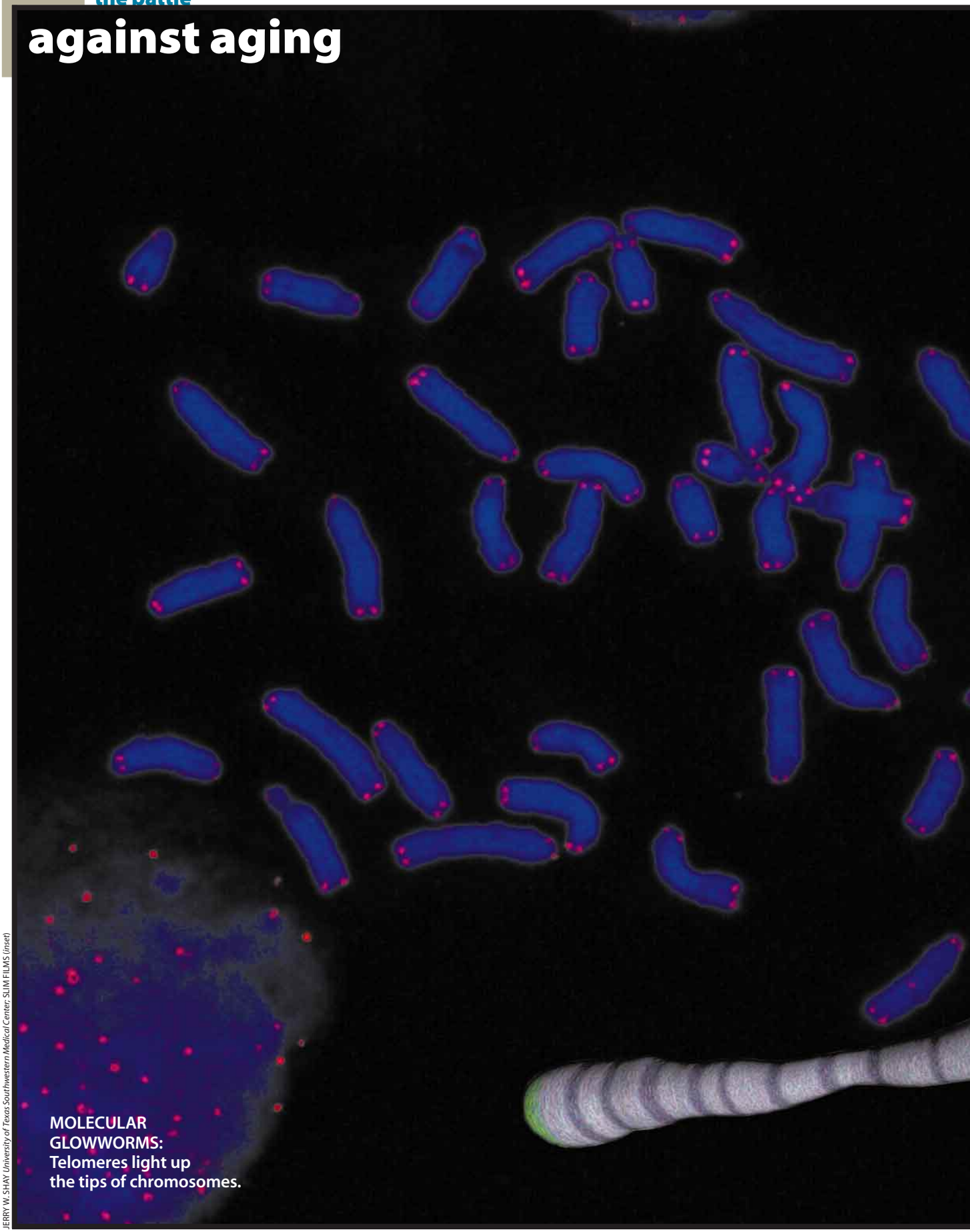
against aging



MOLECULAR GLOWWORMS: Telomeres light up the tips of chromosomes.

JERRY W. SHAY University of Texas Southwestern Medical Center; SLIM FILMS (inset)

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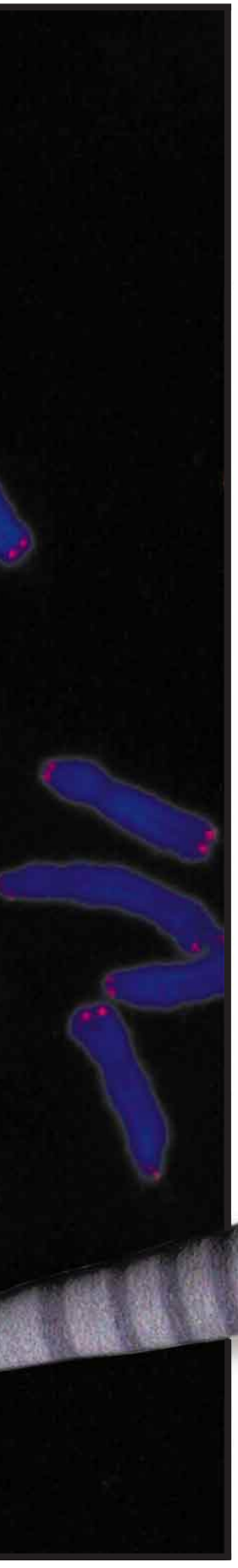
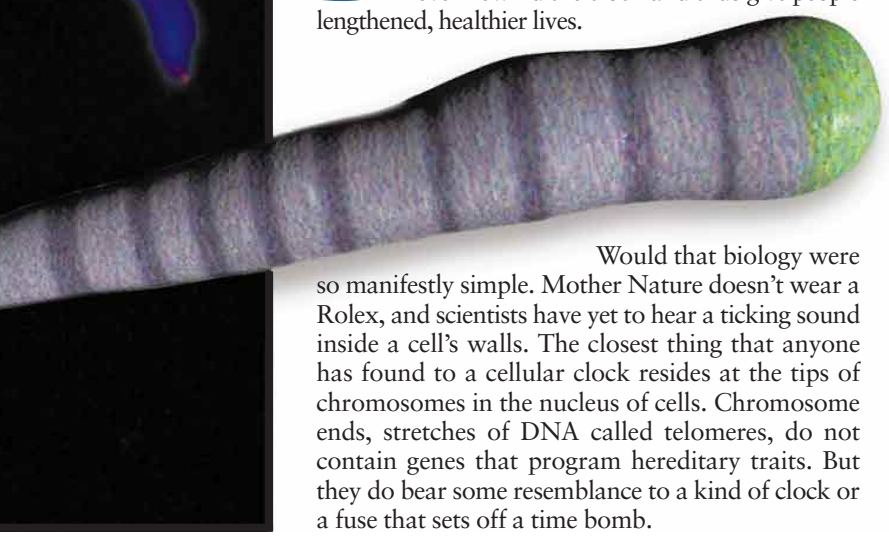
STUDIES OF CLOCKLIKE ELEMENTS IN THE NUCLEUS OF CELLS COULD LEAD TO A RANGE OF THERAPIES THAT MIGHT BOLSTER THE IMMUNE SYSTEM, REVERSE HEART DISEASE, EVEN COMBAT CANCER

counting the lives of a cell

BY EVELYN STRAUSS



Biologists have always warmed to the notion of a cellular alarm clock that would mark off the moments of a cell's life and ring when its time to die had arrived. The existence of such a molecular timepiece might suggest ways to slow the ticking or even rewind the clock and thus give people lengthened, healthier lives.



CAPPING CHROMOSOMES: Telomeres—stretches of DNA and the proteins that bind to them—protect the ends of chromosomes.

Would that biology were so manifestly simple. Mother Nature doesn't wear a Rolex, and scientists have yet to hear a ticking sound inside a cell's walls. The closest thing that anyone has found to a cellular clock resides at the tips of chromosomes in the nucleus of cells. Chromosome ends, stretches of DNA called telomeres, do not contain genes that program hereditary traits. But they do bear some resemblance to a kind of clock or a fuse that sets off a time bomb.

When some human cells are examined in the laboratory, their telomeres shorten each time a cell divides. As a cell divides more than a set number of times, its telomere fuses become too short. At that point, the cell may die, or else a kind of alarm may go off within it that causes the cell to go into a senescent state, in which it ceases multiplying.

Biologists have theorized that cell senescence might have a good side. It could be a defense against cancer, which is marked by uncontrolled cell division. Cells that are unable to regrow their telomeres should stop dividing before they can cause too much mischief. Yet telomere shrinkage could conceivably disrupt the repair and replenishment of tissues, making them age. "It's absolutely clear that the aging of many human cells in culture is a telomere-dependent process," states Titia de Lange of the Rockefeller University. "The question is how significant it is for aging of the whole organism." Does the behavior of cells that reside in the test tube have

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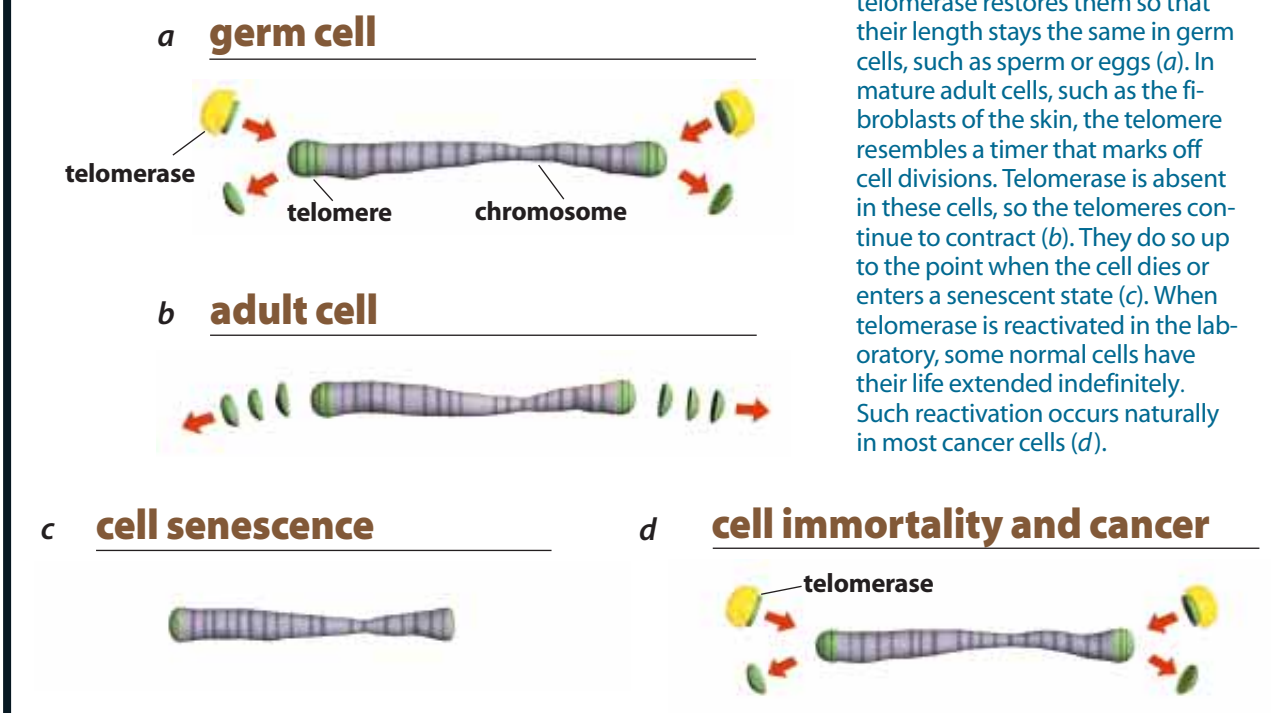
the long and the short
of telomeres



LIKE A CLOCK: Telomeres, the tips of chromosomes, shorten every time a cell divides, but the enzyme telomerase restores them so that their length stays the same in germ cells, such as sperm or eggs (*a*). In mature adult cells, such as the fibroblasts of the skin, the telomere resembles a timer that marks off cell divisions. Telomerase is absent in these cells, so the telomeres continue to contract (*b*). They do so up to the point when the cell dies or enters a senescent state (*c*). When telomerase is reactivated in the laboratory, some normal cells have their life extended indefinitely. Such reactivation occurs naturally in most cancer cells (*d*).

SLIM FILMS

anything at all to do with how we age?

Scientists have now begun to explore de Lange's question. In animal studies, they are examining whether the wearing down of the telomere fuse can illuminate the process of growing old or at least explain why some organs start to deteriorate. "No one's ever proved that short telomeres cause aging," acknowledges Jerry W. Shay of the University of Texas Southwestern Medical Center. "The only way to do that is to prevent it from happening, and that's what needs to be done—but there's already some pretty suggestive evidence."

Some hallmarks of aging in humans, such as hair loss or skin wrinkling, are easy to understand as consequences of cells' inability to multiply, says de Lange, because the cells that replace hair and rejuvenate skin divide throughout a person's lifetime. Similarly, the immune system gradually loses its ability to bounce back. Even "nonrenewing" tissue might replenish itself. "We know now that even in brains, you can get new neurons," says Calvin B. Harley of the biotechnology firm Geron Corporation. "In every tissue except possibly the heart, cells divide. Some divide slowly, but we live a long time."

Age-related deterioration in these and other tissue types could result from cells running out of steam because of telomere loss, Harley asserts. At sharp turns in blood vessels, where turbulent blood flow wears out tissue and thus requires restoration, the telomeres are shorter than in long, straight stretches.

Walking the Telomere Plank

To explore methodically what telomeres mean to an intact animal, scientists genetically engineered mice so that they have unusually short telomeres. At first glance, you might think the animals in these experiments belong in a murine nursing home. They go gray, their hair thins, their skin turns papery, and they die young. Furthermore, they're infertile, presumably because the cells destined to become eggs or sperm can't reproduce or survive optimally. Some cells have "walked the telomere plank," says Ronald A. DePinho of Harvard Medical School. The mice have short telomeres, he says, and their stem cells can't multiply as many times as they usually do. Stem cells give rise to many cell types, such as the various components of skin.

But the physiology of these mice doesn't mimic all aspects of aging, DePinho cautions. "We don't see an increase in cataracts or osteoporosis" or other pathology typical of old animals. "Telomere attrition does not precipitate a classical premature aging syndrome. But we do believe it influences an absolutely critical aspect of getting old—the ability of organisms to counteract acute and chronic stress."

As individuals age, their organs can still function adequately, but they re-

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spond poorly when confronted by chemical or physical insults. "The difference between a young person and an old person is a diminished capacity to respond to major environmental stresses," DePinho notes. The mice in his experiments healed poorly after enduring various shocks—minor surgery and chemotherapy, for example. "Wound healing requires robust proliferative responses, and so does replenishing the blood supply after chemo wipes out white blood cells," he explains.

How relevant these results are to humans remains to be seen, however. "Mice are not little people," DePinho points out. Unlike human cells, for instance, mouse cells' telomeres do not grow shorter, so it is implausible that mice normally age as a result of the gradual shriveling of the ends of their chromosomes.

Although no one has directly tested the relation between telomeres and human aging or disease, nature may have inadvertently conducted a relevant experiment. Telomere defects might underlie a rare inherited disorder called dyskeratosis congenita (DKC). Patients with the disorder carry abnormally short telomeres. They have discolored-looking skin that doesn't renew itself well.They become anemic in their teens, and many die from infections. "We can see what happens in a telomere-deficient person," says Kathleen Collins of the University of California at Berkeley, warning that the results need to be confirmed in more than the two families studied so far.

INDERJEET DOKAL *Hammersmith Hospital and Imperial College School of Medicine (top and bottom)*

TELOMERE DEFECTS: A patient suffering from dyskeratosis congenita, which is characterized by aberrant telomeres, shows signs of premature aging.

The cell types that are most compromised in this disease, Collins says, are ones that in humans produce a telomere-restoring enzyme called telomerase. This enzyme resides in the stem cells that eventually become sperm and eggs (which need to multiply throughout a large part of a person's life). It is also present in certain other cells—those used to revitalize the blood and skin, for example—but not in most other types. "What the disease tells us," Collins says, "is that there are some cell types that need to turn on telomerase in a normal human life span."

Using telomerase to maintain the ends of chromosomes—and so heal damaged or tired organs in people of any age—has become a focus of research at Geron and a number of academic research laboratories. So far adding telomerase in the laboratory has increased the healthy life span of human cells from the skin, blood vessels, eyes, muscles and immune system, and Geron is currently targeting these and other cell types to develop new therapies.

Telomerase therapy might one day help generate a new supply of skin and blood cells to treat lesions that don't heal or to enhance the waning immunity of aging blood cells, both common problems of old age. Although some stem cells produce telomerase, there's not enough to maintain telomere length when demand for reproduction is particularly high, according to some researchers. Adding telomerase to stem cells that generate new blood and skin cells could permit them to survive longer and continue dividing to produce new cells virtually indefinitely.

Earlier this year researchers reported that a telomerase-based treatment allowed cells to stay alive in culture and that they functioned properly when transplanted back into a different animal. Someday a similar therapy that extracts cells from a patient, adds telomerase and then reimplants them into the donor's body might avert the risk of immune rejection. The telomerase could

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also spur cells lining veins and arteries to make new blood vessels when plaque buildup blocks arteries, according to scientists at Geron.

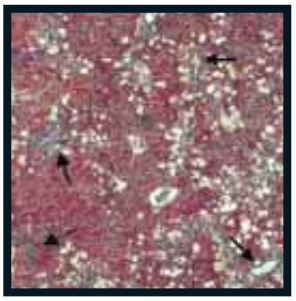
One approach may eventually involve gene therapy—in which the gene that gives rise to telomerase is delivered to the desired site in the body. Because telomeres are shorter in cirrhotic livers than in healthy ones—possibly a result of too many cycles of cell damage and subsequent regeneration—this method might increase the replicative capacity of surviving liver cells and thus could renew livers damaged by alcohol or disease. DePinho recently inserted the gene for telomerase into mice with artificially induced liver damage. Production of the enzyme reduced injury in the animals from cirrhosis of the liver.

Of course, gene therapy of any type confronts the same safety concerns that arose after the death last year of a patient receiving treatment for a rare metabolic disease unrelated to telomeres. As an alternative to gene therapy, researchers are seeking drugs that might control the gene when it is already present in cells so it can be turned on and off at will.

Human trials of telomerase therapy have yet to begin, and it's not clear what the first treatment will be. Telomere shortening, Harley posits, is probably "a fundamental underlying pathway that contributes to many diseases." And he adds: "The technology isn't decades away—it's on the horizon. We hope to be in clinical trials within a handful of years."

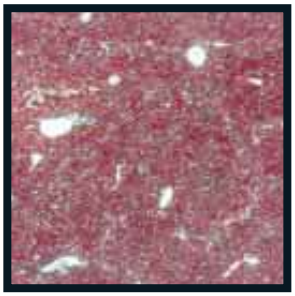
Harley's views have yet to achieve a consensus among molecular biologists and gerontologists. But even Harley derides the popular misconception that telomere research will increase longevity. "We're not saying that we have a maximum life span of 120 because of telomere loss and that if you were to activate telomerase in a controlled way, you'd live to be 200," Harley clarifies, adding that halting telomere loss may, however, alleviate age-related diseases.

Questions remain about whether telomere shortening actually makes cells deteriorate except in a laboratory dish. Even where scientists have established a causal link between telomere biology and cellular life span, they have done it in cells removed from the body. The strongest proof that telomerase reinvigorates tissues in an animal would be to produce the enzyme in cells that normally shut it off and then determine that it can extend life in those cells. Such experiments are under way in mice, but the results have yet to be reported.



SAFEGUARD: Damage to a mouse liver at the onset of cirrhosis (*arrows in top image*) was not as dire in another mouse liver that received the gene for telomerase (*bottom*).

Telomerase therapy may one day prevent liver cirrhosis.



"To connect telomere shortening with aging may be a brilliant stroke of insight, or it may represent a distraction, having little to do with human aging," remarks Robert A. Weinberg of the Massachusetts Institute of Technology's Whitehead Institute. "To show a connection, you'd want to see that organs are giving out because they've lost telomeres. It would be wonderful if there was such a simple molecular explanation of the aging process, but biology doesn't necessarily oblige."

Even if it does help rejuvenate certain tissue, telomerase will not likely serve as an all-purpose antiaging preparation. The enzyme should not have an effect on cells that do not divide in the mature body, many of which are involved in processes of aging. "A lot of what we think of as aging takes place in nonreproducing cells," de Lange observes. "Alzheimer's is generally viewed as an important aspect of human aging. I don't think there's any reason to believe that those plaques [damage to the brain produced by the disease] have anything to do with loss of the proliferative abilities of nerve cells."

Not all human cells are likely to snap awake with the addition of telomerase; freeing some types from the chains of mortality (at least in the test tube) requires additional genetic alterations. Furthermore, some cell types senesce within a small number of generations—long before their telomeres have decayed significantly—indicating that other mechanisms can arrest growth. Even if you could make a cell immortal, you might not want to. Adding telomerase to a cell can have dire consequences. "You have to confront the reality that you're creating a cell that is one step closer to cancer," Weinberg says. "Cell mortality is an important impediment to cancer."

The Cancer Connection

Tumor cells, after all, can live forever. According to several studies, telomerase plays a critical role in maintaining, if not triggering, this disease that affects the elderly in disproportionate numbers. Telomerase by itself does not cause cancer: healthy cells err in multiple ways in their slide toward malignancy. But cancer cells do seem to have figured out how to use telomerase to sustain the abnormal cell division that is the hallmark of the malady. According to some researchers, they achieve this unchecked multiplication by activating telomerase or restoring telomere length by other mechanisms. In contrast to most normal cells, about 85 to 90

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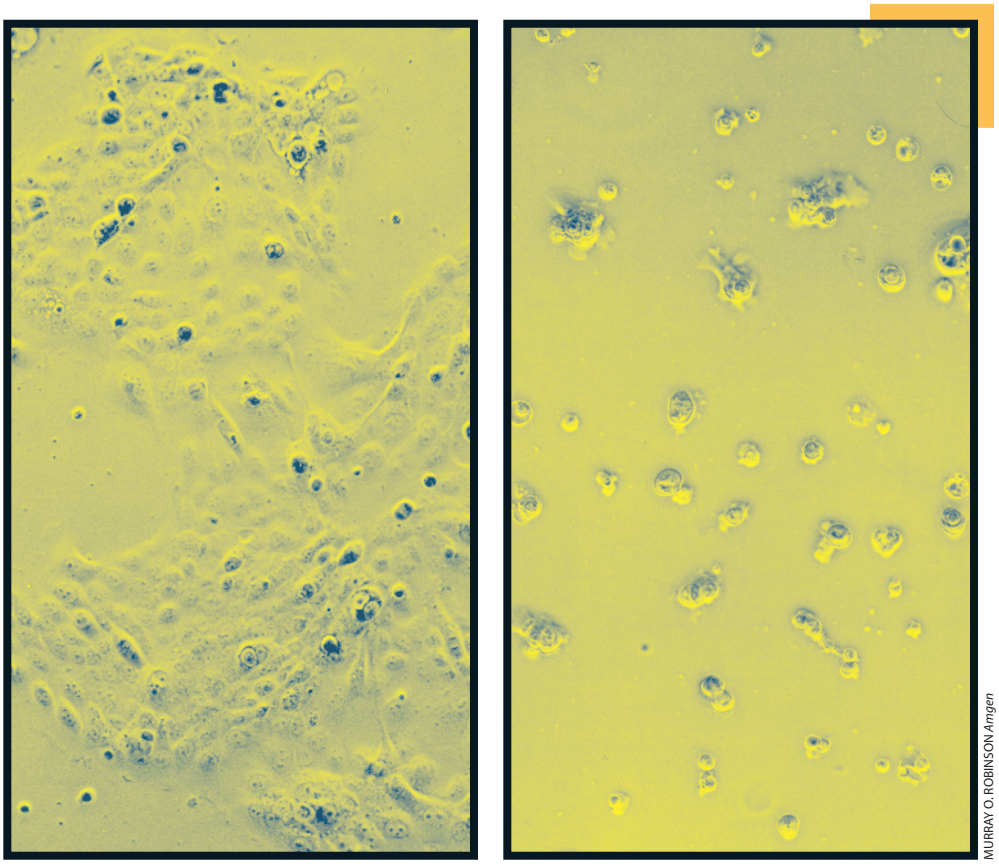

MURRAY O. ROBINSON *Amgen*

TUMOR INHIBITOR: Cancer cells thrive when the enzyme telomerase is present (*left*). When it is inhibited, the cells change shape and die (*right*).

percent of tumor cells produce telomerase. And treatments that inactivate telomerase kill cancer cells growing in the lab. "That is formal proof that the ongoing activities of telomerase are essential for proliferation in cancer cells," Weinberg concludes.

A drug or genetic therapy that blocked telomerase might quash the unbridled growth of malignant cells. "It's too early to tell, but based on the available evidence, we think the prospects look good for antitelomerase therapy," asserts Murray O. Robinson of Amgen, a biotechnology firm. "It's incredibly exciting that telomerase is a property that crosses virtually all tumor types, because such drugs might be universal chemotherapeutic agents." The idea of developing them is "not just a pie-in-the-sky hope," he continues. "We know if we inhibit this enzyme we can kill tumor cells, and we know we can make inhibitors against other enzymes of this type."

Some scientists expect that telomere-based anticancer strategies will trigger fewer severe side effects than other chemotherapies. Most healthy cells do not carry telomerase, and they would thus be expected to remain unaffected if a drug were to inhibit the enzyme. Normal cells that do produce telomerase—sperm, egg and stem cells—start out with much longer telomeres than about 50 percent of cancers, so cancer cells should stop dividing before they do. This aspect of telomere biology might provide a means to attack malignant cells without interfering with the normal renewing activities of other cells.

Still, some researchers worry that tumors might develop resistance to antitelomerase therapies. Mice that lack telomerase can still form tumors, and about 10 to 15 percent of human tumors apparently do not produce the enzyme, suggesting that not all cancer cells need it. "There's clearly some kind of bypass pathway in mammalian cells," warns Carol W. Greider of the Johns Hopkins University School of Medicine. Other researchers argue that resistance of this type is unlikely to pose a serious problem, because none of the investigations have discovered it in the types of cells from which most cancers arise.

Telomere research has created a paradox that must still be resolved: the enzyme telomerase might revive an aging liver. Alternatively, it might promote cancers. Only clinical trials will ultimately resolve the many lingering questions about which, if any, types of telomere therapies might succeed for aging or cancer. The original hope that we could trick Father Time into giving us immortality by manipulating telomeres will probably prove naive, however. We cannot simply rewind telomeres like an old-fashioned Swiss watch. But studying the tips of chromosomes as they fritter away may still yield insights into how the cell, the basic biological unit, grows old. That accomplishment alone would mark a fundamental contribution to the science of human aging.

Evelyn Strauss, *a molecular biologist turned science writer, freelances from Santa Cruz, Calif., and is a correspondent for* Science *magazine.*

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Descriptions of research at the biotechnology company Geron on telomerase for age-related disorders can be found at www.geron.com on the World Wide Web.

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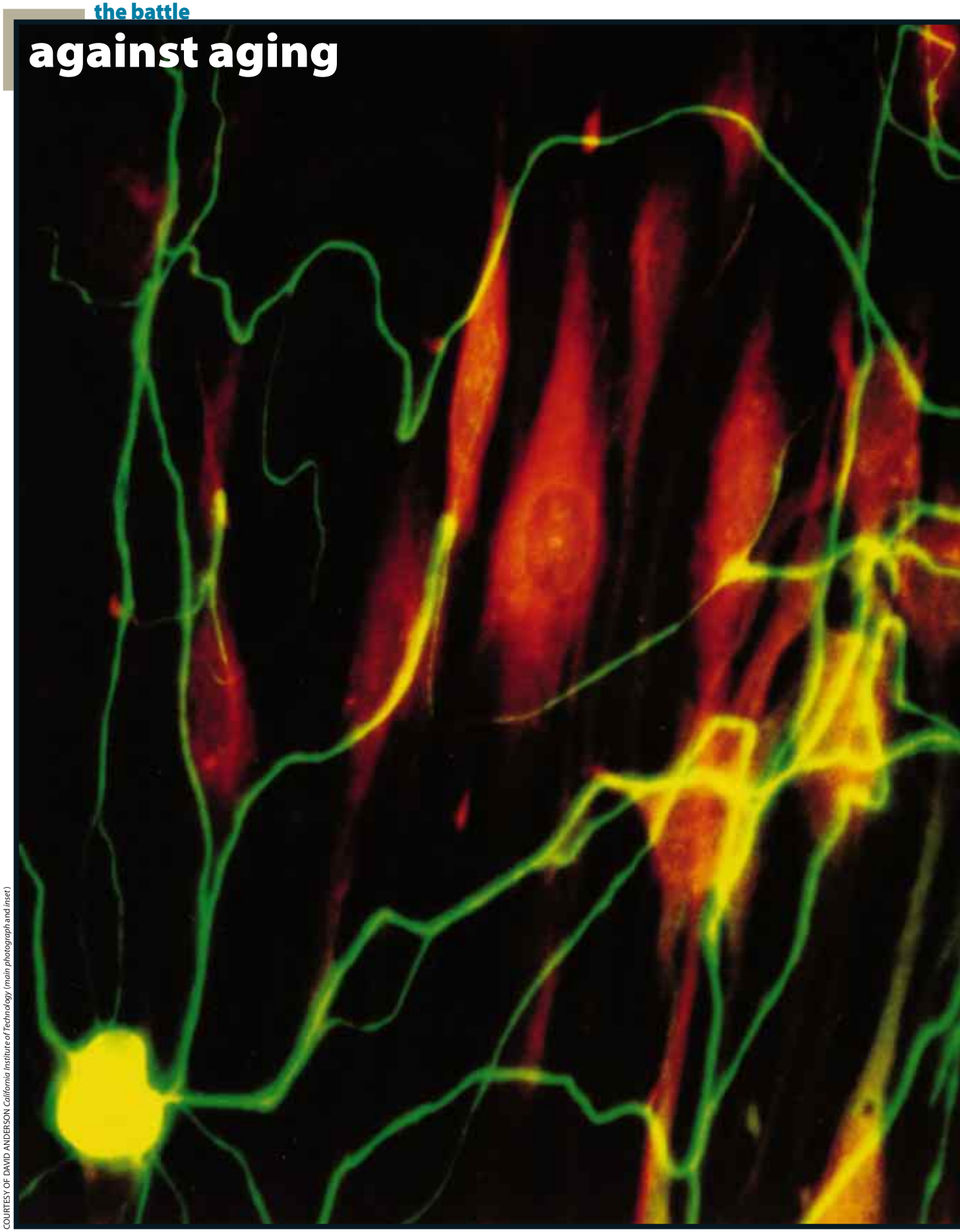
the battle

against aging



COURTESY OF DAVID ANDERSON *California Institute of Technology (main photograph and inset)*

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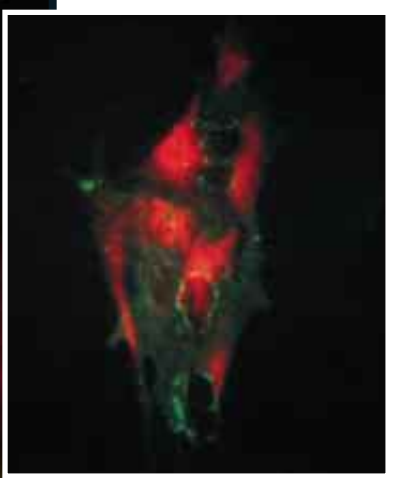
STEM CELLS MIGHT ROUTINELY REPAIR OUR WORN-OUT TISSUE, IF SOCIETY ACCEPTS THIS APPROACH

mother nature's menders

BY MIKE MAY

In the 1970s *The Six Million Dollar Man* television program opened each week by showing a terrible accident that turned astronaut Steve Austin into "a man barely alive." Then we heard: "Gentlemen, we can rebuild him. We have the technology." The idea intrigued us but seemed centuries away. It's not. An explosion of work surrounding stem cells, which can differentiate into many other cell types, raises hope for medical repairs beyond our imagination—mending a damaged heart, fixing a failing liver, improving a forgetful brain and, most exciting, significantly extending life. Instead of using bionic parts, like the ones that made Steve Austin stronger and faster, this technology could provide us with longer and healthier lives by enabling us to control our natural repair mechanisms.

This emerging field takes advantage of a cell that may



TWO FROM ONE: Neural stem cells (*inset*) can give rise to differing cell types: neurons (*yellow*), which are wired to their neighbors, and glia (*red*), nucleated structures in the background.

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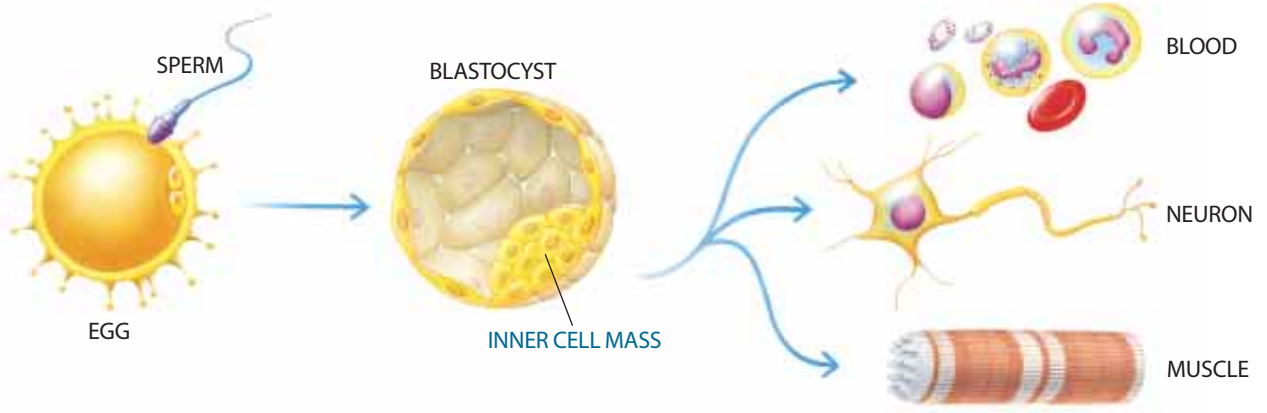
origin of a stem cell



SPECIALIZATION: Some scientists consider a stem cell to arise when a sperm fertilizes an egg (*left*). Others think it originates in the inner cell mass of the blastocyst, a hollow sphere that emerges after several cell divisions (*center*). Either way, stem cells can differentiate into unique cell types, such as muscle, blood and nerve tissue (*right*).

TOMO NARASHIMA

emerge from the moment of conception. When a sperm cell works its way into an egg during fertilization, some scientists consider the result to be a stem cell. Other researchers consider stem cells to appear after several cell divisions that turn a fertilized egg into a hollow sphere of cells called a blastocyst. That sphere includes a region called the inner cell mass, consisting of a group of stem cells. Wherever stem cells first arise, they can branch out in many directions. A stem cell holds all the information it needs to make bone, blood, brain—any part of a human body. It can also copy itself to maintain a stock of stem cells.

Many of us imagine that a human body builds up most of its cells and tissues early in life, and then everything begins to fall apart, cell by cell. New findings prove otherwise. Stem cells busily work away throughout our lives, acting like an army of housekeepers, cleaning up a little mess here and repairing some damage there. In some cases, a group of these cells work together to perform gargantuan tasks. For example, the stem cells located in bone marrow must replace more than one billion red blood cells every day. Such rebuilding might be going on constantly all over the body. Stem cells also seem to make new cells continuously for bone, liver, heart, muscle and even the brain, where scientists long thought that we were incapable of generating new cells.

Bodily Tune-ups

Stem cells serve as a natural defense against aging. As things wear out, these cells can repair some damage. As we get older, though, the failures in our bodies apparently overrun the stem cells. Consequently, we decline—getting slower, weaker, more forgetful. Nevertheless, many scientists believe that they could slow these processes with a stem cell tune-up. Moreover, a regular dose of jazzed-up stem cells might fight off degeneration and keep us living a longer and healthier life.

The inherent qualities of stem cells have drawn tremendous attention to them. To be sure, some scientists take the *Six Million Dollar Man* approach and try to fabricate new parts from exotic metals and space-age polymers. You can already get an artificial hip joint, an implantable device to help with hearing loss, and replacement valves for your heart. Some groups are even pursuing an electronic retina. But why rely on so many different parts—essentially a new fix for every problem—when you could use stem cells instead? Stem cells might be a cure-all of sorts, basically one-stop shopping for repairing anything that ails you.

Despite the recent interest in stem cells, they are not entirely new in medical therapies. Physicians have been extending human lives for years by including stem cells in some treatments. For example, some forms of cancer, such as childhood leukemia, require such a devastating dose of chemotherapy that it destroys a patient's bone marrow. A bone marrow transplant can restore a patient's blood-making capability, presumably because it provides a new supply of blood-making stem cells. When physicians started using bone marrow transplants, though, no one had seen a human stem cell. They just assumed that such cells existed.

In late 1998 all that changed. Two sets of researchers in the U.S.—John Gearhart's group at Johns Hopkins University and James Thomson's team at the University of Wisconsin–Madison—isolated human stem cells. These results shook up science and society, raising hope for therapeutic uses of stem cells

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as well as a range of ethical questions.

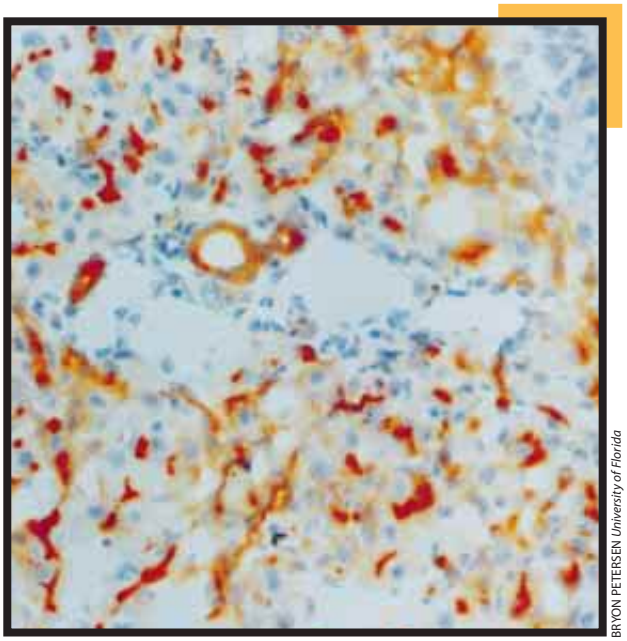
After the first reports, investigators launched a parade of promising animal experiments. Evan Snyder of Harvard Medical School has shown that neural stem cells seek out damaged areas of a mouse's cortex—the highest centers of the brain—and make new neurons there. He has very preliminary evidence that neural stem cells can do this in primates, too. "We're starting to move our way up the evolutionary ladder," Snyder says, "suggesting that this really may be a kind of intervention or kind of application that we could use." He also mentions evidence that neural stem cells could generate new neurons in other areas of the brain and even in the spinal cord. If human neural stem cells can go to damaged areas in the nervous system and create neurons there, such a technique might fend off Parkinson's disease, amyotrophic lateral sclerosis (better known as Lou Gehrig's disease) or old-age dementia.

Tissue Flipping

These findings seem to be cropping up in one organ after another. For instance, Bryon Petersen of the University of Florida says his work in rats showed that a cell that originated in the bone marrow could travel to the liver, incorporate into that organ and become a functioning liver cell. Presumably, that bone marrow cell was a blood-making stem cell. As Ronald McKay of the National Institute of Neurological Disorders and Strokes explains, "One really exciting thing that's going on in the field at the moment is, in fact, we're sort of discovering that the stem cells that have been defined in different tissues are actually capable of flipping from one tissue to another." McKay notes that researchers are not absolutely sure that the flipping really goes on in stem cells but adds that "there are cells that are capable of giving rise to the cells of another tissue: brain into blood, brain into muscle, pancreas into liver, muscle into blood."

Still, scientists must answer a crucial question: Do the new cells really work? In most cases, it's hard to tell. Just because a stem cell ends up in the brain and turns into what looks exactly like a neuron doesn't mean that it works properly. Still, McKay and his colleagues did show at least one case in which new neurons did work. First, they caused a Parkinson's-like disease in rats by killing neurons that communicate through a neurotransmitter called dopamine. Then they obtained neural stem cells from rat embryos and injected the cells into the Parkinsonian adult rats. In less than three months the normal movement in most of the treated rats improved by about 75 percent.

Over this incredibly promising work looms a controversy that threatens some stem cell research. It all revolves around one word: embryo. In essence, scientists talk about two general classes of stem cells, ones that come from embryos and ones from adults. Some people would never condone using embryos in any way because of ethical beliefs. If you can get stem cells from adults, though, surely this entire problem can be resolved by forgoing the use of embryonic stem cells. But, as Thomson explains, "the embryonic stem cells have the potential to form anything. It's not clear what the developmental potential is of some of these other stem cells." In other words, an embryonic stem cell can do it all—make any cell needed—and adult stem cells might be limited to making a few kinds of cells. Furthermore, adult stem cells could be partially worn out, so that they would not offer the full rejuvenating benefits of embryonic ones.



A NEW IDENTITY: Stem cells in bone marrow transplanted from one rat to another developed into cells that produced a functional enzyme (*red-orange areas*) in the liver of the recipient animal.

BRYON PETERSEN *University of Florida*

Despite all the potential benefits of using embryonic stem cells, working with them remains off-limits for researchers receiving federal funding for their studies, as all powerful laboratories do. A ban put in place by the U.S. Congress on the use of federal money means that research is confined to the narrow universe of just a few private biotechnology companies—Geron Corporation and Advanced Cell Technology being the leaders. Progress in the field is slower than it might be without the prohibition. But the funding environment may change.

In November 1998 President Bill Clinton asked the National Bioethics Advisory Commission to investigate the medical and ethical issues behind embryonic stem cells. Its report concluded: "[T]he Commission believes that federal funding for the use and derivation of [embryonic stem] cells should be limited to two sources of such material: cadaveric fetal tissue [from naturally aborted fetuses] and embryos remaining after infertility treatments." The report thus encouraged federal funding for certain approaches to stem cell research. Then, in December 1999, the National Institutes of Health, the primary source of U.S. biomedical funding, published a draft for guidelines on stem cell research, which went out for public comment. These documents suggest that the outlook for at least limited federal support has become less bleak.

But the National Bioethics Advisory

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the battle
against aging

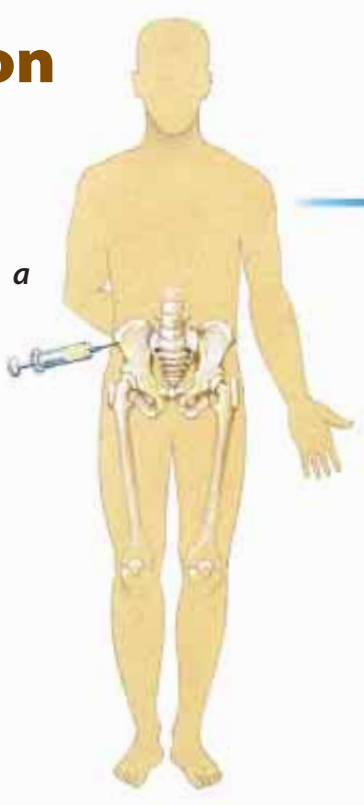
Commission did not endorse an approach called nuclear transfer, which Michael West of Advanced Cell Technology champions. In his technique, researchers remove the nucleus from a cow's egg, implant a human cell—say, a skin cell—inside it and allow it to grow embryonic stem cells. With this system, West and his colleagues might be able to use skin cells—obtained by merely scraping a toothpick across the inside of your cheek—to make embryonic stem cells just for you. That could be important because your immune system might fight off stem cells from anyone else, seeing them as foreign invaders, like a virus. In addition, cow's eggs come cheaply and in large numbers. Still, combining human and cow cells started more than a little disgruntled mooing, because some people see it as a dangerous mixing of species. West defends his approach, saying, "We take the [cow] egg and remove its DNA, so there's no more mixing of species than there is when you drink cow's milk."

In any case, you need West's approach only if your body really is likely to reject foreign stem cells. West says your immune system would search out foreign cells with the efficiency of a hawk hunting a mouse. Thomson, one of the first to isolate human embryonic stem cells, agrees that the body would reject stem cells as it does some organ transplants: "Absolutely. Once they differentiate, they'll become adult cells like any other cell in the body," which would cause them to be rejected. But Thomson's opinion is not universal. One company, Osiris Therapeutics, has found through its studies that foreign stem cells are not cast out by the immune system. "It really doesn't seem to be the case. We don't quite know why that is," says Osiris scientist Mark Pittenger.

Luckily, investigators do agree on some topics. For example, most everyone thinks they could grow these cells in culture and keep them alive essentially forever. About his human embryonic cells, for instance, Thomson says, "We've kept them growing for well over a year. By any measure that we have, they appear to be immortal." And once researchers know how to culture whatever kind of cells they have, they can make incredibly large numbers of them. For example, a single human skin cell can spawn 170 trillion trillion trillion cells. Moreover, farming these cells in culture could reduce the concerns about using embryonic tissue. "One of the things I think people don't like about this is the idea of constantly going back to human embryos and doing the stuff over and over and over again," McKay says. "But technically, we can grow the cells, we can really grow them. I think this is going to be very efficient, so you needn't be concerned that this is going to be a big [embryo] harvesting industry. It's not going to be like that." The recently created WiCell Research Institute—with Thomson as its scientific di-

tissue
rejuvenation

BIOENGINEERING: Companies have already begun to contemplate medical techniques that would use stem cells to reverse the effects of aging on flesh, blood and numerous organs. A sample of bone marrow containing stem cells could be extracted from the pelvis (*a*). The cells could then be grown in a culture (*b*) before being removed, inserted into a blood bag and reinjected into the body (*c*). (The solution would contain both stem cells and progenitor cells, products of stem cells primed to make certain tissue.) In the body, this mixture would home in on locations where they could help revive, say, a damaged liver or kidney. One company, Aastrom Biosciences, is developing a machine that will culture enough stem cells over a 12-day period to make medical uses practical (*photograph*).



EXTRACTION

CULTURING

AASTROM BIOSCIENCES

TOMO NARASHIMA

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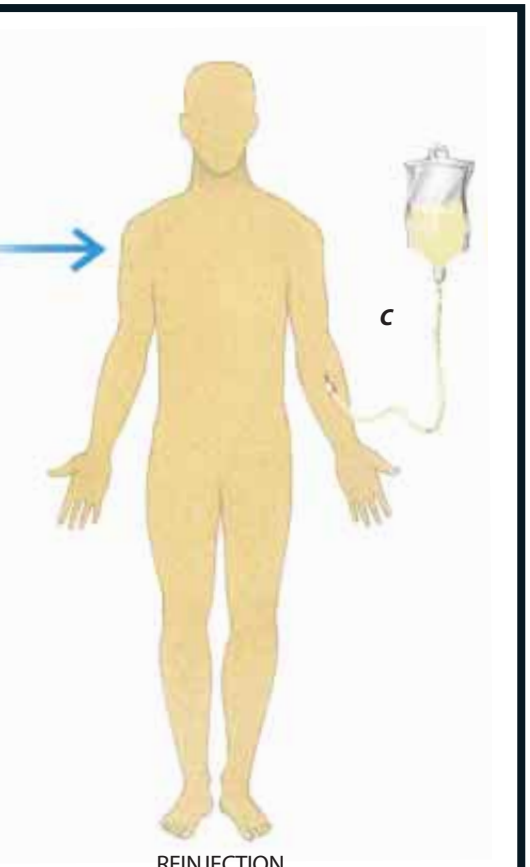
rector—plans to grow and sell human embryonic stem cells for research.

Although physicians already rely somewhat on stem cells—at least for bone marrow transplants—many more clinical applications might lie just over the horizon. Stem cells might be used to repopulate or replace cells devastated by disease. It might even be possible to take a stem cell, nudge it chemically toward making the kind of tissue desired and then control its environment in a way that causes it to build an entire organ. The organ could then be used in someone who needs a transplant, the pinnacle of so-called tissue engineering.

When could some of these stem cell techniques be available? "I think we're going to be moving into clinical trials with human neural stem cells of some type for some disease within two years," Snyder says. That means that stem cell–boosting treatments could be available in five to 10 years. Making entire organs from scratch, however, lies much further in the future. In theory, physicians could get so good at fixing organs with stem cell treatments that such organ fabrication might never be needed.



REINJECTION

Just Hit "Play"

Some companies are already counting on a market in stem cell medicine. For instance, Douglas Armstrong of Aastrom Biosciences describes a machine developed by his company that is primed with a sample of bone marrow or even blood from an umbilical cord, both of which contain stem cells. According to Armstrong, "The equipment operates much like a VCR with a videocassette. The user takes the cassette, pops it into the machine and the machine takes over. Twelve days later the cassette comes back out, goes on another machine and transfers the cell product to a blood bag that's ready for therapy."

The resulting blood bag would contain stem cells as well as so-called progenitor cells, which are products of stem cells that are primed to make specific tissues. A physician could simply inject stem and progenitor cells into the bloodstream, and many of them would home in on locations where they were needed.

Armstrong adds, "It's practical to think we may be entering a future period where all of us put aside a small amount of bone marrow or even our umbilical cord blood when we are born, and then samples of that are grown out into populations and we get infusions of those cells later in life that might, indeed, help us live much longer, healthier lives."

Many hurdles lie between ongoing research and turning stem cell techniques into therapies for humans. "These therapies are brand-new," Thomson says. "There are no precedents for them." Consequently, a researcher can't simply see what stem cell treatments do in rats and mice and then try the same thing in humans. In a hypothetical example, Thomson speculates that a newly discovered technique that cures diabetes in mice might not help human diabetics but instead leave them with a worse disease—pancreatic cancer, for example. In other words, a treatment for a serious but survivable disease could give patients a certain death sentence.

"So you want to make really sure what you're doing isn't worse than the disease you're trying to cure and that there's a lot of safety involved," Thomson continues. "Because the therapies are so new, going straight into humans would be a problem." Much more research on primates and then extensive clinical testing must be completed before new stem cell techniques become available as a routine form of treatment.

Scientists do know that stem cells promise entirely new views of how the human body works. "For me, the absolute true potential of these is more in how it's going to give us a clue to understand the human body," Thomson says. "So even if [stem cells] were never to be used for transplantation purposes, they give you this brand-new scientific model to study. If you're interested in heart disease, you can study populations of human heart cells in tissue culture for the first time on a regular basis.

"I think the transplantation stuff will be important," he goes on, "but someday we'll understand enough about the human body that these transplantation therapies won't be necessary, because it will be possible to cause specific cells to regenerate themselves in ways they don't naturally do, because we will understand how that development normally occurs."

We might never see science rebuild a man with Steve Austin–like techniques. Instead researchers may rebuild us by tweaking systems that our bodies possessed all along—stem cells, the ultimate medical weapons. Now we must wait to see if science and society can agree on ways to use these seemingly magical wonders of biology.

Mike May *lives and works as a freelance writer in Clinton, Conn.*

Further Information

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spare O

HOPE: A bioartificial kidney could someday end the exhausting regimen of dialysis. One prototype (*right*) has been developed by the University of Michigan.

MULVEHILL *The Image Works*

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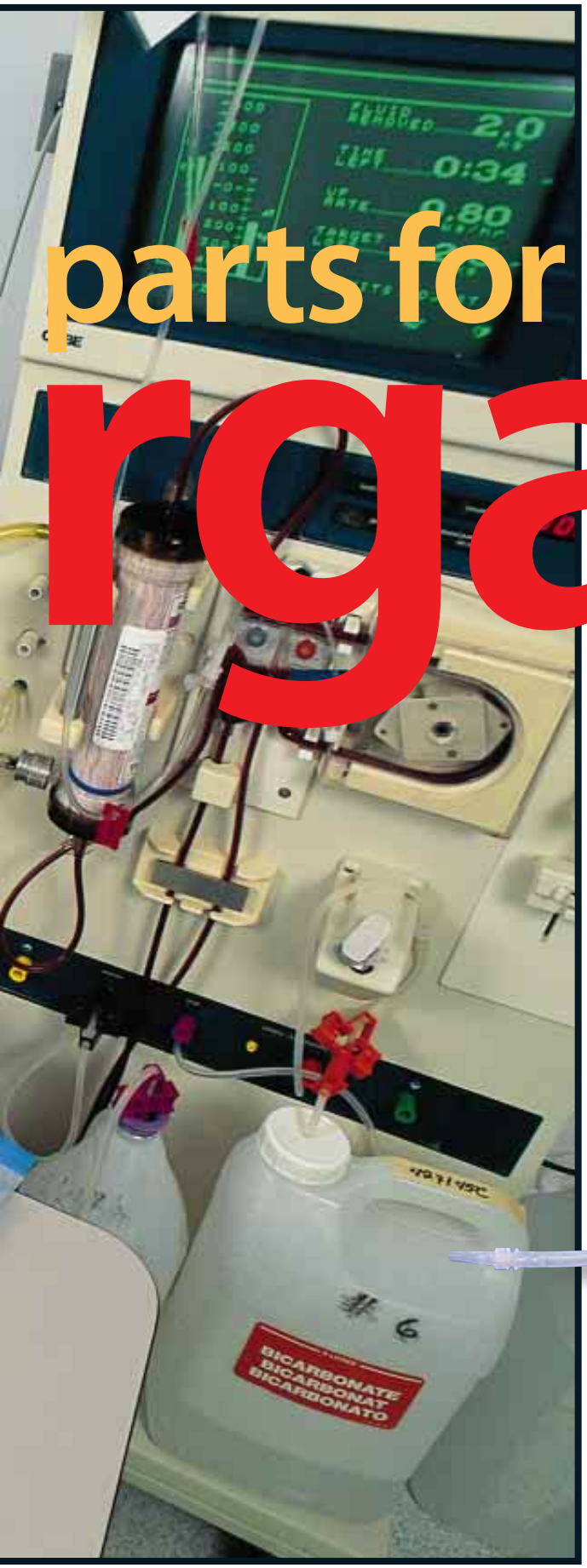


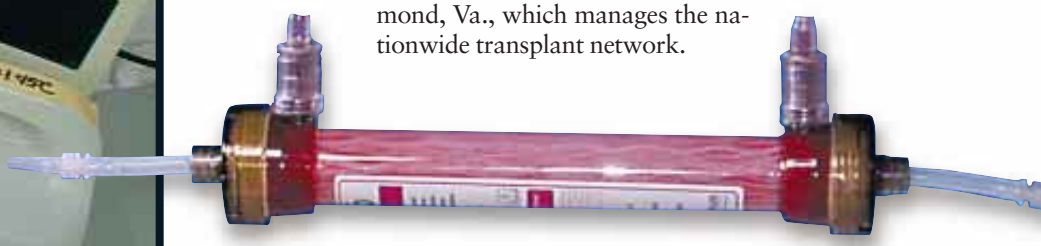
ENGINEERS ARE CREATING ARTIFICIAL REPLACEMENTS FOR FAILING HEARTS, KIDNEYS, PANCREASES AND LIVERS

parts for vital organs

BY DAVID PESCOVITZ

Atherosclerosis, diabetes, cirrhosis, hepatitis and other afflictions kill or disable millions of people every year by ravaging their organs over time. The elderly suffer the greatest toll. Bioartificial organs—a merger of mechanical parts with cells grown in laboratory cultures—could reduce premature death, improve quality of life and serve as vital bridges for seniors waiting for natural-organ transplants.

In the U.S., thousands of people die annually waiting for a transplant, and many thousands more never even make it onto a waiting list, according to the United Network for Organ Sharing in Richmond, Va., which manages the nationwide transplant network.



VA ANN ARBOR HEALTHCARE SYSTEM

Engineering whole organs from scratch using pristine stem cells that can differentiate into any kind of body tissue would, of course, be the ultimate solution. But that is a longer-term prospect. For now, bioartificial organs offer the greatest hope for spare parts that can perform the complex tasks of a kidney, pancreas or liver. "We call these the smart organs," says Bartley P. Griffith, director of the McGowan Center for Artificial Organ Development at the University of Pittsburgh. A heart simply pumps blood through one-way valves. Kidneys, pancreases and livers face the arduous task of

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McGOWAN CENTER, UNIVERSITY OF PITTSBURGH

NEW PUSH: The McGowan Center's prototype artificial heart propels blood with a tiny impeller, rather than the power-hungry pumps used in past attempts to replace the organ.

chemically removing waste from incoming fluids and producing key compounds for the body. "If a heart is thought of as a first-grader," Griffith says, "a kidney is a senior in high school, and a liver is a postdoc."

Despite its "simplicity," building an artificial heart has proved difficult. The image of Barney Clark, recipient of the first Jarvik-7 artificial heart in 1982, was telling; his mechanical heart, which replaced his failed natural heart, was connected by hoses to a large, thumping pneumatic bellows outside his body that did the actual pumping. The unit had to be plugged into the wall, limiting Clark's movement. When Clark and a second artificial heart patient, William Schroeder, died within two years as a result of infections and strokes caused by blood clots, the public's hope in the technology died with them.

It took years for researchers to rethink their approach and miniaturize components. Instead of a full-blown replacement, recent devices have attempted to assist a failing heart until a transplant can be found. The left ventricular assist device (LVAD), the foremost example, is now in clinical use. A surgeon implants it into the abdomen, where it pumps blood that has been diverted from the left ventricle, one of the heart's four main chambers that pump blood. The device is powered by a small console or portable battery pack outside the body. The LVAD solves only some heart problems and still requires a power cable that passes through the patient's skin, but it buys crucial time.

LVAD progress has renewed interest in a new generation of artificial hearts. They are smaller and more efficient because they move blood in a fundamentally different manner. Instead of pumping with flexing diaphragms as did the previous generation, they have a tiny spinning impeller that propels the blood like a boat propeller moves water. The McGowan Center uses this approach in its Streamliner artificial heart, designed to be placed in the abdomen and to push blood through the natural heart and arteries using a pair of tubes. Inductive coupling could transfer energy from a coil attached to a battery worn on a belt to a secondary coil and battery implanted under the skin. The subcutaneous battery would then send power to the artificial organ over a thin wire.

The Streamliner may be the Cadillac of artificial hearts. The oblong device, made of titanium, is about four inches long, two inches across and weighs several ounces. It features an impeller suspended internally with magnets. "This eliminates the risk of failure because of bearings wearing out," says Griffith, who adds that the Streamliner faces at least 18 more months of well-funded development before it is ready for testing.

Other leading research teams are using the turbine approach in experimental LVADs. Thermo Cardiosystems is working with the McGowan Center, and Micromed Technology has partnered with the Baylor Medical Center.

Developing a "dumb" organ like the heart is a major engineering challenge, yet it pales in comparison with the complexity of building organs that have biochemical brains. To craft "smart" bioartificial organs like the kidney, pancreas and liver, experts must combine electrical, mechanical and tissue engineering. The strategy thus far is to take organ cells from humans or pigs, grow them in a culture medium, then load them into a bioreactor—a box or tube in which they are kept alive with oxygen and nutrients. The bioreactor is inserted into a larger machine outside the body. A patient's blood is diverted via tubes through the bioreactor, where it is cleansed—similar to the setup of today's kidney dialysis machines.

"Of course, the trick would be to understand the cell culture science and engineer the bioreactor well enough to implant one of these organs," Griffith notes. "I think we're 10 years away from that at least." Closer to fruition, he believes, is a "get out of trouble" bioartificial kidney, worn like a fanny pack, that could keep a patient alive during the wait for a donated human organ.

Beyond the Dialysis Machine

Diabetes and hypertension—the leading causes of kidney disease—plague the elderly. Today there are more than 40,000 Americans waiting for a kidney transplant. They must undergo dialysis or hemofiltration for hours at a stretch, multiple times each week. The regimen is exhausting. Just as vexing is that the machines can do only half the task at hand. While the kidney filters urea waste products from the blood, its tubules must also reclaim 98 percent of the filtrate, returning important sugars, salts and other substances to the body. Dialysis machines just can't pull off the second step.

By combining mechanical devices with engineered tissue, a bioartificial kidney could perform the entire function. Nephrologist David Humes and his colleagues at the University of Michigan have cultured proximal tubule cells, which handle the bulk of filtrate reclamation, from pig kidneys. The cells are enmeshed along hair-thin plastic fibers that line the inside of a polycarbonate filtration cartridge about 10.5 inches long and 1.4 inches in diameter. The cartridge is housed in a larger machine. As the patient's blood is pumped through

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the bioartificial kidney, the engineered cells filter out urea while returning the useful compounds.

Trials of the new system conducted on dogs last year were successful, and Humes is hoping for approval from the Food and Drug Administration to begin human trials later this year. "At this point, this is a temporary device for acute kidney failure," he explains. "But we're working on devices that have both filtration and a tubule element that could be wearable. We're in a prototype stage."

According to Humes, the first-generation wearable renal assist device could diminish a patient's dialysis time by 30 to 50 percent and someday possibly eliminate it entirely. "The first dialysis machine was a huge 10-by-4-foot cylinder," Humes says. "Our cartridges do the same thing, but you can hold them in your hand." If fabrication advances make possible even more miniaturization, he adds, he and his team might be able to "devise one of these for implantation."

SWEET: Now in development, Circe Biomedical's PancreAssist would automatically monitor blood sugar levels and dispense insulin for diabetics.

CIRCE BIOMEDICAL

An implantable bioartificial device to assist a malfunctioning pancreas would create a similar revolution in the treatment of insulin-dependent diabetics. At present, diabetics must follow a strict daily regimen of self-administered tests to check blood sugar levels and one or more insulin injections to pick up the slack of a weak pancreas. But "because there is no effective feedback mechanism" for the level of insulin required, injection "is done as a best guess," says Barry Solomon, president and chief scientific officer of Circe Biomedical in Lexington, Mass. The resulting large swings in glucose levels are thought to lead to the major complications of diabetes—vascular disease, retinal disease and heart disease.

The goal is to automate the system. Existing implantable insulin pumps tend to leak, and electronic glucose sensors are notorious for failing after little more than a month inside the body. But the real shortfall is that today's systems cannot supply the feedback information needed to administer precise and properly timed dosages.

Circe's PancreAssist system is designed to solve the problem. It is an insulin-on-demand system based on the body's own chemistry. Now in preclinical development, PancreAssist is an implantable tubular membrane surrounded by insulin-producing islets, all contained in a plastic housing. As the patient's blood flows through the center of the tube, the islets, harvested from pigs, detect changes in the patient's glucose levels and respond by producing insulin when needed. The insulin diffuses across the membrane into the person's blood. The membrane prevents white blood cells and antibodies from attacking the porcine cells, so immunosuppressant drugs are not needed. The unit, half the size of a hockey puck and weighing only a few ounces, will be implanted near the kidney. "Because we're using cells that not only have the ability to produce insulin but also can sense and regulate that production in response to glucose levels, we're essentially reproducing what the natural pancreas does," Solomon explains.

An early version of the PancreAssist proved effective in animals several years ago, but a reengineering of the vascular graft was required before human studies could begin. Solomon hopes the slimmed-down system will be proved on animals and ready for human clinical trials within two years.

Letting the Liver Regenerate

The challenge is greater for a bioartificial liver to replace a natural one damaged by diseases and insults such as hepatitis C and alcoholism. A healthy liver metabolizes toxins, produces bile, regulates the balance of many hormones and manufactures blood-clotting proteins. Designing an organ to accomplish all these complex tasks is daunting. But a device may be needed to replace these functions only for a short time, says Achilles Demetriou, a bioartificial liver pioneer who is chairman of the surgery department at the Cedars-Sinai Medical Center in Los Angeles. "The liver has such a remarkable capacity to regenerate that temporary support could result in complete recovery of the injured organ," Demetriou points out. If a damaged liver could be relieved of all its duties for just one week, it would have a good chance of repairing itself. There is currently no machine that can take over the organ's function, however.

The goal, therefore, is a bioartificial organ that can bridge the repair time. Several companies are pursuing state-of-the-art work, including Organogenesis in Canton, Mass., developers of FDA-approved lab-grown skin, and Circe Biomedical, whose HepatAssist system was developed in collaboration with Demetriou.

HepatAssist is undergoing phase II and III clinical trials in liver transplant centers around the U.S. It uses pig liver cells in a bioreactor to remove toxins

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the cryonics gamble

No "corpses" reside at the Alcor Life Extension Foundation. Just three dozen "patients" entombed at a rock-hard 320 degrees Fahrenheit below zero who have bet that future physicians will have the technology to "reanimate" them. When each one was at death's door, a friend or family member had phoned Alcor's CryoTransport team. The outfit rushed to the scene. Once a doctor had pronounced the subject clinically dead, the team put the deceased on ice, pumped the body full of medications and solutions and transported it to Alcor headquarters in Scottsdale, Ariz.

The team then circulated glycerol, used as antifreeze, into the major arteries to prevent damaging ice crystals from forming among cells. The patient was then placed in a "dewar"—a tall metal thermos that is filled with liquid nitrogen. The patients stand there today in wait. But don't dare compare them to mummies. Cryonics, Alcor insists, has nothing to do with "bringing people back from the dead."

TIMOTHY ARCHIBALD

YOU BET YOUR LIFE: At her death, Christine Peterson will be frozen in a tank by Alcor, run by Linda Chamberlain (*right*), in hopes she can be revived and repaired.

Freeze now, revive later is certainly one way to attempt to extend your longevity. The first Alcor "member" has been frozen since 1976. "If you're feeling good and you enjoy life, it's not a matter of figuring out why you should do this," says Christine Peterson, a 42-year-old writer and Alcor subscriber. "It's more a question of why you would want to check out."

Nice theory—but there's a catch. Someone someday will have to figure out how to reconstruct your body, mind and soul. And at present neither Alcor nor anyone else knows how to do it. Therein lies the gamble.

Peterson's not worried. She believes a cure for aging will come along before she needs to be frozen. "For people around my age and younger, cryonics is more like backup insurance," she says. If a fix doesn't materialize, then she's betting that nanotechnology will bring her back from the deep freeze. Nanotechnology is one of her life's passions. She has penned a book about it and is married to scientist K. Eric Drexler, a maverick nanotechnology evangelist. The believers say that one day thousands of nanobots—microscopic robots one billionth of a meter long—will be able to travel through your body *Fantastic Voyage*–style, repairing cells to fix whatever ails you. The army of dutiful nanobots would repair widespread cellular damage caused by the freezing, rejuvenate your brain cells and rebuild your tired old body, cell by cell, into something new.

But no one has crafted a single nanobot. And although nanotechnology is all the rage in the popular press, many scientists ridicule molecular robots as little more than the ruminations of science-fiction aficionados.

Peterson has such faith in nanotechnology that she has signed up for Alcor's neuropreservation service—freezing just her head. It'll simply be attached to a more youthful body when it's thawed. Nanotechnology will fix any complications from her recapitation and will subsequently keep her new body youthful forever. Her mother, husband, friends and colleagues such as artificial-intelligence researcher Marvin Minsky will be glad to see it; all of them are signed up with Alcor.

Putting your frozen corpse—er, body—in Alcor's care doesn't come cheap. The flat fee is $120,000. Whether that's enough for the needed half-century of minding isn't clear. Charles Platt, a writer of science fact and fiction and director

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IRWIN DAUGHERTY *AP Photo/Mesa Tribune*

of the CryoCare Foundation, which subcontracts freezing, isn't expecting a cryonics patient to be successfully resuscitated for at least 60 years.

If we all could be frozen and defrosted, the earth might become a crowded place. Peterson has an otherworldly solution for that, too: colonize outer space. Her vision of a space-faring society, common among her future-minded peers, is reminiscent of the late LSD guru Timothy Leary's prescription for the human race: SMI^{2}LE, an acronym for "space migration, intelligence increase and life extension."

Indeed, Leary was arguably the most famous advocate of cryonics. (Contrary to rumors, Walt Disney was cremated after his death in 1966, and Michael Jackson has never publicly announced plans to take a liquid-nitrogen bath.) But if, as English scholar Samuel Johnson noted, the prospect of one's imminent demise tends to concentrate the mind wonderfully, then eternity on ice may lose some of its allure. During his final hours of life, Leary abruptly changed his plans for cold storage. His stated reason, according to friends who were at his bedside: "Waking up in the future surrounded by a bunch of men in white lab coats holding clipboards didn't sound like so much fun." —*D.P.*

from the blood of patients, in a technique similar to Humes's bioartificial kidney. A cylindrical plastic cartridge 14 inches long and 2.5 inches in diameter, lined with engineered cells, fits into a larger machine. A patient's blood passes through it for cleansing. Patients undergo six-hour sessions for seven consecutive days. "By then," Demetriou says, the hope is that either "their liver recovers and takes over or they receive a transplant."

HepatAssist is intended to serve solely as a bridge. An implantable liver replacement, Demetriou believes, will probably have to be engineered from stem cells, a venture he asserts will be "orders of magnitude more complex" than those for other organs.

In the meantime, whichever bioartificial organs emerge may face competition from other organ-replacement approaches that are also advancing, notes Peter Stock, associate professor of transplant surgery at the University of California at San Francisco. Most anticipated, perhaps, is xenotransplantation, in which organs harvested from transgenic pigs or primates could be transplanted into humans. The organs would be endowed with certain human genes and engineered to not induce immune rejection. Various attempts to fix faulty organs by altering genes directly are under way, too.

Whether tomorrow's spare organs are built around bioartificial cartridges, pig innards or stem cells will in the end be determined by lab work and by safety and effectiveness questions that get hashed out during the FDA approval process. But no matter which technology beats the organ shortage, the ultimate prize will go to the individual who gets a new lease on life after a visit to the human body shop of the future.

David Pescovitz *writes frequently for* Scientific American *and is a contributing editor at* Wired *magazine.*

Further Information

American Heart Association
(www. americanheart.org).

McGowan Center for Artificial Organ Development
(www.upmc.edu/mcgowan).

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against aging

OLD YOUNG PEOPLE: Hutchinson-Gilford syndrome patients often die by their early teens from heart disease or stroke.

W. TED BROWN *Institute for Basic Research in Developmental Disabilities*

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CHILDREN WITH DISEASES OF THE ELDERLY AND STUDIES OF GENES THAT EXTEND LIFE SPAN IN ANIMALS ARE OPENING A WINDOW ON HOW WE AGE

# of hyperaging and methuselah genes

BY EVELYN STRAUSS

Three-year-old Sam likes to feel starfish in his hands, and you can just forget about changing the subject when he's discussing planets. But Sam is not quite your average toddler. He's almost bald, his seven teeth don't align properly, and he is smaller than his peers. So far these are the only clues that he has Hutchinson-Gilford syndrome, a rare genetic disorder that mimics some aspects of aging.

No one can predict what course Sam's disease will take, but children with Hutchinson-Gilford syndrome typically develop arthritis and grow slowly. Their skin becomes thin, and age spots and prominent veins emerge. Most acquire severe atherosclerosis that can thwart blood flow to the brain and other organs. About 50 percent of afflicted children die of heart disease or stroke by their early teens.

When Sam's mother isn't talking to him about Neil Armstrong and Buzz Aldrin, she's in the laboratory, looking for the biochemical basis of her son's disease. Leslie B. Gordon's work on Hutchinson-Gilford syndrome—and research on other related disorders—may have implications far beyond finding a cure for a rare disease. It might also provide clues about the normal human aging process and yield insight into diseases common to old age, such as atherosclerosis, which could lead to new avenues of research for treatments that prolong life.

Hutchinson-Gilford syndrome is one of several human progerias; "progeria" means premature aging. Very little is known about the disease, and the condition is extremely rare—only about 100 cases have been documented since it was first described in 1886. Although the disease appears to be caused by a genetic defect, it doesn't run in families, suggesting that the mutation occurs randomly in egg or sperm cells or at some point after fertilization. Because researchers can't track the gene through relatives, this disorder doesn't lend itself to traditional gene-hunting approaches.

So Gordon, a research associate in the department of anatomy and cell biology at Tufts University School of Medicine, is taking a different tack. She's focusing on the one consistent difference between Hutchinson-Gilford patients and healthy children: sick kids have much higher levels of a particular compound—hyaluronic acid (HA)—in their urine. HA is necessary for life because it helps hold tissue together, but too much of it might be a bad thing, Gordon says. People with another form of progeria, called Werner syndrome, also have high levels of HA, and its concentrations creep up in elderly people, too.

A Trickle of Evidence

Plaques that build up in the blood vessels of people who die of heart disease are steeped in HA. "Whether it's cause or effect, no one really knows," Gordon says. "These kids have these same plaques throughout their bodies, and that's what plays a major role in causing heart attacks and strokes."

The idea that HA contributes to heart disease is not new, but work in this area has been fostered recently by new analytical tools. In this relatively unexplored area of research, Gordon is trying to follow the trickle of evidence to its source. She wants to find out whether the disease grows more severe as HA levels rise and to establish whether the chemical does indeed promote plaque formation. If such a connection were confirmed, it could lead to therapies that fight both Hutchinson-Gilford syndrome and cardiovascular disease by lowering HA levels. "Any treatments that help these children will

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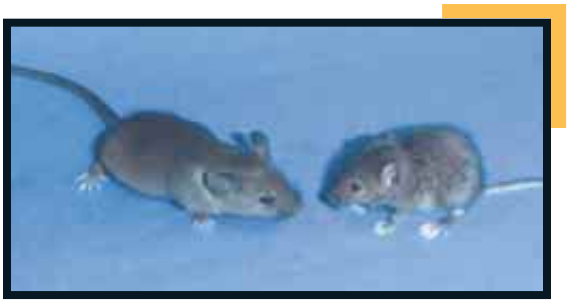
very likely help millions of people with cardiovascular disease and potentially other problems associated with aging," she says.

In another classical premature aging disease, Werner syndrome (WS), symptoms don't begin until adolescence or early adulthood. In this syndrome, hair thins and goes gray, skin wrinkles, and muscles atrophy. Individuals with this condition suffer from cataracts, diabetes, heart disease and other afflictions that don't typically strike until old age.

Although people with Hutchinson-Gilford and WS look old and share many ailments with geriatric patients, the physiological changes overlap only partially with how people usually age.



MAKOTO KURO-O University of Texas Southwestern Medical Center at Dallas

DODDERING RODENT: A *klotho* mutant mouse (*right*) has a small, bent back, unlike a normal mouse (*left*), and a range of age-related disorders, such as atherosclerosis and osteoporosis.

WS sufferers experience a high incidence of cancer, for example, but "they include rare, weird cancers that you don't see too often," says George M. Martin of the University of Washington.

Still, these disorders can provide some intriguing insights, says W. Ted Brown of the Institute for Basic Research in Developmental Disabilities in Staten Island, N.Y. "Mutations in one gene can produce a set of effects that dramatically resemble aging. That implies that relatively few genes could be controlling aging."

Several years ago scientists tracked down the gene responsible for WS. In its healthy form the gene encodes a protein that unwinds DNA, presumably so other proteins that manipulate DNA can wriggle between the strands to do their work. No one yet knows exactly how a defective version of this gene, which would give rise to a faulty protein, could lead to WS. But many ideas are floating around.

In test-tube experiments, WS cells are much more susceptible than normal to harm from a compound that is toxic to DNA. These results suggest that the abnormal WS protein might fail to repair damaged DNA.

And that's just one thought. Studies on a yeast protein that resembles the WS protein have suggested that it undermines DNA integrity in other ways. A mutation in a yeast gene that encodes this protein shortens life span. In cells carrying the altered gene, DNA is cut after it loops into circles, and the ends stick together. The resulting DNA circles contribute to the cell's eventual demise. No one has detected similar DNA rings in cells of people with WS or from old individuals. Some researchers have conjectured, however, that the normal WS protein quashes formation of aberrant DNA structures in humans, a process that might go awry when the gene suffers a mutation.

Already studies on WS have spurred investigators to think about new ways of looking at common disorders of human aging. Perhaps DNA damage from subtle but common variations in the WS gene may predispose people to vascular disease, cataracts and diabetes, even if they don't suffer from a full-blown form of the disease.

The big limitation of studying humans, of course, is that you can't manipulate people as you can laboratory animals. Enter a mutant mouse strain that is afflicted at a young age with many of the diseases common to older humans. The defect in the responsible mouse gene—called *klotho*, after the goddess in Greek mythology who spins the thread of life—accelerates the onset of disorders such as atherosclerosis and osteoporosis.

Researchers have isolated the *klotho* gene from both mice and humans. The human *klotho* lies in a region of the chromosome with no known genetic disorders. Because mice with defective *klotho* exhibit some aspects of premature aging, the gene may be analogous to progeria genes, such as those responsible for Hutchinson-Gilford and Werner syndromes. It's even possible that *klotho* is the yet to be revealed gene that underlies Hutchinson-Gilford. "It would be interesting to see if Hutchinson-Gilford patients have a mutation in the *klotho* gene," says Makoto Kuro-o of the University of Texas Southwestern Medical Center at Dallas.

Antiaging Hormone

Based on an analysis of *klotho*'s DNA and the symptoms exhibited by the mice, Kuro-o hypothesizes that the mutated gene encodes an aberrant protein that circulates in the blood and triggers age-related processes in different tissues—perhaps a buildup of plaque in blood vessels. If so, the normal version of the protein might do the opposite—serving as what Kuro-o calls an "antiaging hormone." The idea of such a blood-borne factor that might keep at least some tissues healthy is a new concept for mammalian aging, Kuro-o says. He is trying to identify the molecules with which the klotho protein interacts in tissues and to figure out how cells with defective *klotho* behave differently from normal cells.

When healthy versions of genes such as *klotho* or the one underlying WS go haywire, they expedite an organism's demise. Studying these mutations and disorders may well yield insight into particular illnesses and conditions of old age. But they will probably not shed much light on one of the most important questions surrounding aging research—that is, how scientists might move beyond simply fighting diseases of old age to finding ways of extending life span beyond the current maximum limit of about 120 years.

To go further, investigators have begun to examine how overproducing some proteins prolongs the lives of microbes, flies and mammals. In yeast, extra servings of a protein called Sir2 lengthen lifetime, increasing the number of times the organism can duplicate. In contrast, yeast harboring a defect in Sir2 has a curtailed life span.

Yeast Sir2 keeps large stretches of genes turned off. Perhaps, as organisms age, they lose their ability to silence genes effectively, suggests Leonard P. Guarente

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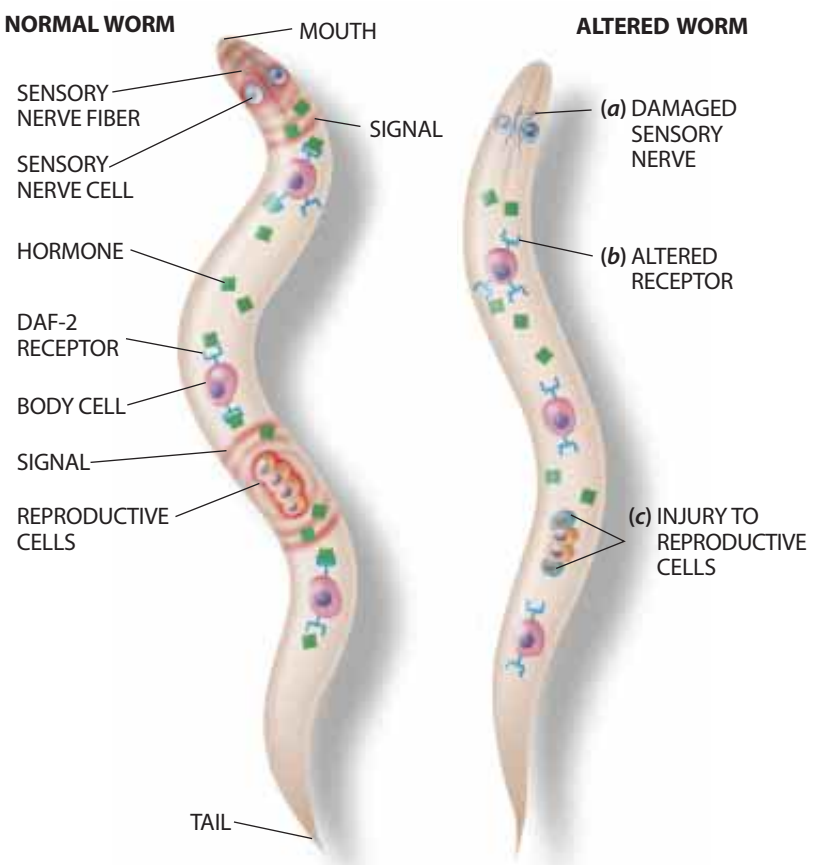
long live the worms



CELL TWEAKING: The reproductive and sensory systems of the worm *Caenorhabditis elegans* send signals affecting activity of hormones that stimulate the daf-2 receptor on certain cells (*left*). Experiments suggest that those hormones influence longevity. Manipulated worms (*right*) live longer than normal when their sensory nerves are cut (*a*), the hormone receptor is genetically inactivated (*b*) or particular reproductive cells are injured (*c*).

JOHN W. KARAPELOU

of the Massachusetts Institute of Technology. In this scenario, activation of particular genes would spur changes in physiology that lead to aging. Mammals, too, carry a Sir2-like protein, and it may function in a manner similar to that of the one in yeast. Adding to the evidence, results in mice suggest that loss of silencing may promote mouse aging, says Bruce M. Howard of the National Institutes of Health. Other genes increase life span when overproduced as well. In flies, extra copies of enzymes that neutralize oxidants, harmful oxygen-containing molecules, extend the insects' lifetimes.

If natural aging results from general deterioration of various bodily functions, it might seem surprising that single mutations could dramatically lengthen life. Last year, though, researchers reported a strain of mouse that can live almost a third longer than normal because of a mutation in one gene.

It's now known that single gene mutations in other organisms can lengthen life span. Several long-lived worms carry mutations in a gene involved in a process that appears to use chemical signals to trigger activities inside cells. The gene resembles one in humans that encodes a protein that receives messages from hormones such as insulin and growth factors. Researchers believe genetic alterations in the worms that render this protein insensitive to such hormones increase their life span. No one knows exactly how this works, but the mutant worms—known as daf-2 mutants—increase production of enzymes that protect cells from oxidants [*see illustration at left*].

Studying worms suggests a general strategy for antiaging therapies. "If aging is regulated by a hormone, it can probably be slowed by a hormone," says Gary B. Ruvkun of Harvard Medical School. A drug that regulates such a hormone, however, may be a mixed blessing. Some but not all mutations predicted to decrease hormone signaling in worms also slow metabolism. As for possible antiaging treatments, what's the point of being alive if your metabolism is so slow that you're essentially asleep? Still, it's possible that scientists could find a hormone that affects longevity but not metabolism. Drugs that target such a hormone might prolong life without making people sluggish. Furthermore, many daf-2 mutants remain healthy and vigorous for much longer than their normal counterparts do, suggesting that extending life without slowing anyone down might be relatively easy, says Cynthia J. Kenyon of the University of California at San Francisco.

Every organism has its idiosyncrasies, but many basic truths of nature apply across the boundaries of species. The discovery of hormones that apparently control life span, or some aspect of age-related diseases in worms and mice, hints at a general biological mechanism for health and longevity that extends beyond any single organism. In the future, we may be able to apply lessons learned from our simpler cohabitants to stay younger and healthier ourselves.

Evelyn Strauss *is a science writer based in Santa Cruz, Calif.*

Further Information

Basic information about progeria can be found at the **Progeria Research Foundation** site at http://progeriaresearch.org on the World Wide Web.

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thwarting

major killers

preventing

TWO CLUES: Studies of identical twins—including Sonja Buth and Wilma Bruno (*right*)—in which only one sibling (Buth) has Alzheimer's may determine to what extent genes and the environment contribute to the disease.

JAMES ARONOVSKY *Zuma Press*

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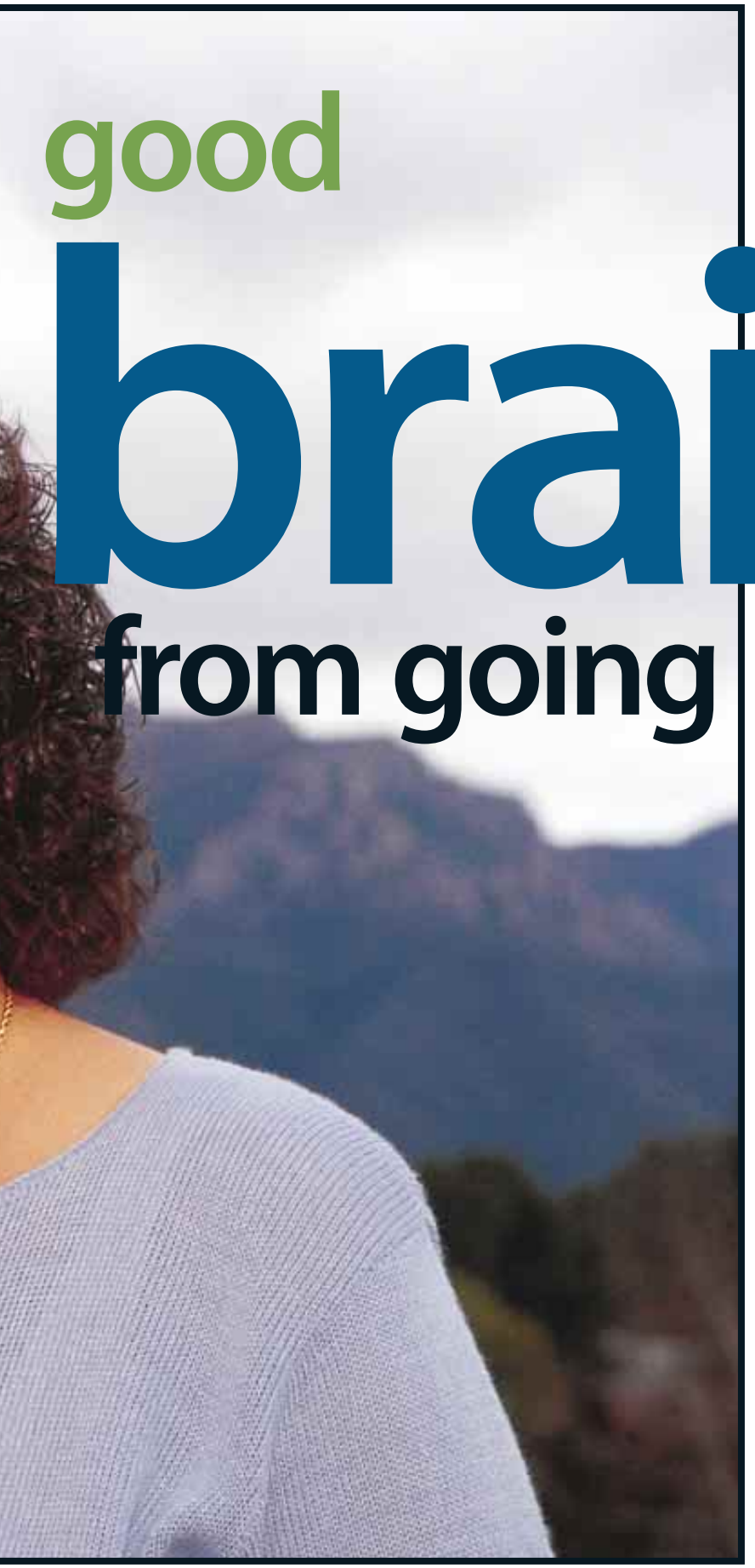

good brains from going bad

THE FIGHT AGAINST TWO LIFE-ROBBING DISEASES, ALZHEIMER'S AND PARKINSON'S, HAS JUST BEGUN

BY MIA SCHMIEDESKAMP

It's hard to believe now, but 30 years ago the average layman *and* the average doctor thought that "senility" was the result of either normal aging or hardening of the arteries. "What do you expect from an old person?" people would say. Mercifully, science has enlightened this rather Dickensian view. Today we may be close to understanding what causes the major neurological diseases of old age, which ravage mental and physical function—the very stuff of life—and in their extreme form can kill.

But that does not mean we've found cures for the four million Americans suffering from Alzheimer's disease and the one million with Parkinson's. The numbers could swell fourfold by 2040 as baby boomers reach old age. Legions of us worship at the temples of Physical Fitness and Cooking Light, in an attempt to ensure strong bodies at retirement. But what can we do when it's our brains that betray us?

The silent siege of Alzheimer's causes a relentless deterioration of memory and bodily control. The disease is a formidable foe. Most Alzheimer's patients are in their 70s and beyond, and those who survive into its final stages lose the ability to speak, walk, even lift their head as their brain slowly shuts

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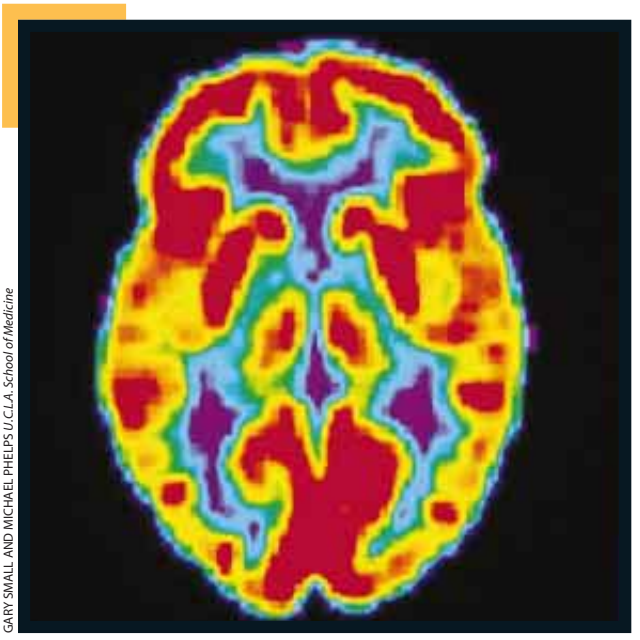
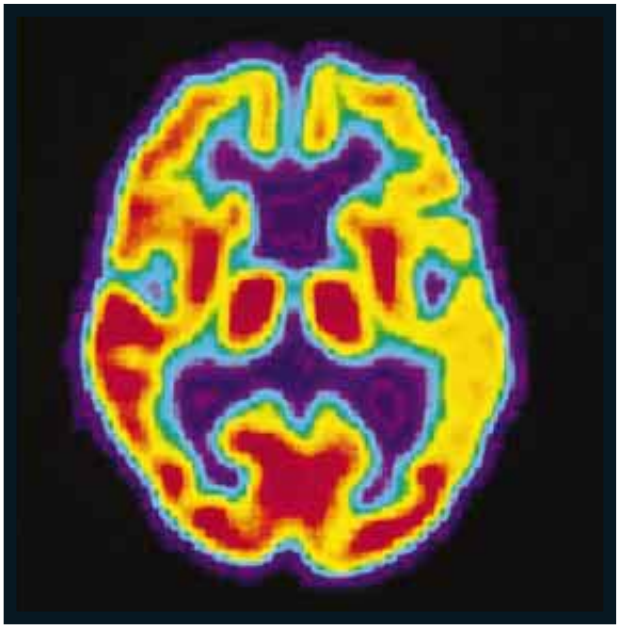


GARY SMALL AND MICHAEL PHELPS U.C.L.A. School of Medicine

BRAIN SCAN: Reds and yellows indicate a brain's glucose metabolism. There is a progressive decrease from a normal older person (*left*) to mild Alzheimer's (*below*) to advanced disease (*right*), which resembles activity in an infant's brain (*far right*).



down. Given how debilitating the physical throes are, it is confounding that the disease first appears years earlier as mental troubles such as chronic forgetfulness and difficulty handling routine chores. Indeed, the onset is so elusive that doctors are only now determining where normal aging of the brain stops and Alzheimer's begins.

The borderland is a state called mild cognitive impairment (MCI). Individuals with MCI aren't demented, but they do perform worse than their peers on memory tests. They sense they are forgetful, and somebody close to them has probably noticed it, too. Otherwise, they do quite well, although demanding tasks such as mastering new technology may prove challenging.

People who meet the criteria for MCI will evolve to clinical Alzheimer's disease at a rate of 10 to 15 percent a year, according to Ronald Petersen, director of the Mayo Alzheimer's Disease Center. "That's in contrast to normal elderly people,"—without MCI—"who do so at a rate of 1 to 2 percent a year," he says. Barry Reisberg, clinical director of the Silverstein Aging and Dementia Research Center at New York University, finds similar trends. When he tracked people with MCI in their early 70s, about two thirds progressed to Alzheimer's within four years.

Images of the brain can help pinpoint those most at risk. The hippocampus—a structure closely tied to memory—atrophies and shrinks in Alzheimer's patients. The decline is evident even during MCI. Someday a combination of memory tests and magnetic resonance imaging may offer early warnings to those destined for Alzheimer's—valuable information if drugs are developed that can prevent the disease or stop its progression.

Elderly people who feel forgetful but perform well in cognitive tests—Petersen refers to them affectionately as "the worried well"—develop Alzheimer's at much lower rates, about 12 percent over four years in Reisberg's study. All that's necessary, Reisberg says, is "to reassure them."

Older people these days do seem quick to diagnose themselves or loved ones as having Alzheimer's when they are just experiencing simple forgetfulness. The knee-jerk response is in part the result of stepped-up media coverage.

So what *should* set off alarms? Failure to remember important items with increasing frequency, Petersen says—"things that you would have remembered without question six months ago"—especially if other people also say they see a change in you. "It's not that you misplaced your keys," adds Richard Mohs of the Mount Sinai School of Medicine. "It's that you can't figure out what you would do to get them back."

Mohs points out that everybody gets more forgetful with age. "The rate at which people can put new information into memory does slow down. When they say, 'I forget more,' it's usually that they just didn't learn it quite as well." Elderly people can boost memory by taking extra time and care to learn new information.

Rays of Hope

Once Alzheimer's is diagnosed, families can brace for the future, but the medical profession finds itself at something of a loss. Neurotransmitter-boosting drugs such as Aricept help about 50 to 70 percent of patients, according to Peter Rabins of the Johns Hopkins School of Medicine, but their efforts are modest. Rabins says, "I ask families to think back to what the person was able to do seven or eight months ago; that's an average improvement." Although this reprieve is precious, it's unclear if any improvement can last longer than a few months. For now, managing Alzheimer's consists mainly of

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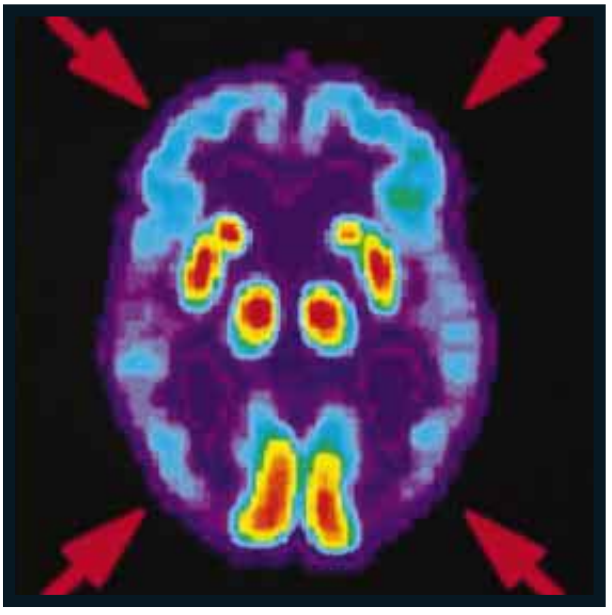
emotional and practical support, plus strategies to help patients retain skills and live a full life [*see box on next page*].

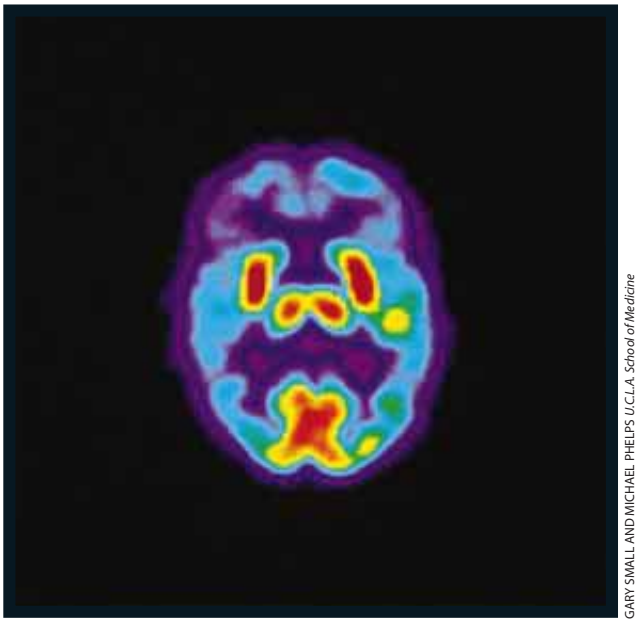
An ounce of prevention may be worth a pound of cure. Various studies, including a landmark University of Kentucky study of elderly nuns belonging to the order of the School Sisters of Notre Dame, suggest that the brain's ability to resist dementia is greater if it has been mentally stimulated throughout life. "If you don't use it, you lose it," exhorts the University of Kentucky's William Markesbery, part neuropathologist, part personal trainer.

Richard Mayeux, director of the Taub Institute on Alzheimer's Disease and the Aging Brain at Columbia University, also finds that people with complex jobs have reduced risk of Alzheimer's no matter their education—suggesting again that intellectual challenge throughout life is important. Mohs of Mount Sinai suggests exercising the brain by reading, taking classes and joining intellectually engaging clubs.



Caring for the body is a good idea, too. People who are aerobically fit tend to suffer less cognitive decline with normal aging. Intriguingly, when Fred H. Gage of the Salk Institute for Biological Studies in La Jolla, Calif., allowed mice to run at will—about five kilometers a day on average—they generated many more new neurons in their hippocampi compared with their cage-potato counterparts. Others have found that prolonged stress actually leads to hippocampal atrophy.

The search for ways to slow or prevent Alzheimer's is widening. The nuns, as well as identical twins and a group of women in upper Manhattan, are the primary test subjects. Many of the School Sisters nuns donate their brains to the University of Kentucky's Sanders-Brown Center on Aging; Markesbery, the center's director, has examined them and others. One remarkable thing he sees are organs rife with the lesions characteristic of Alzheimer's—from individuals who were not demented.



GARY SMALL AND MICHAEL PHELPS *U.C.L.A. School of Medicine*

Perhaps these brains had something extra in reserve, or maybe they avoided stroke. Dementia from vascular disease alone is fairly uncommon in the U.S. But among nuns with the brain lesions of Alzheimer's, those who also had tiny strokes were more likely to be demented. To lessen the risk of stroke, Markesbery advises people to eat right, exercise, not smoke, and keep blood pressure and diabetes under control—good advice in any case.

Aging women in upper Manhattan point the way to another possible protection: estrogen. "For women who took estrogen in the postmenopausal period, the risk of developing Alzheimer's disease subsequently was reduced by half," explains Mayeux, who monitored about 1,100 New York City women for up to five years for the appearance of Alzheimer's. The women who had taken estrogen for longer than a year showed the greatest benefit.

Studies in Minnesota, Baltimore and Italy have yielded similar results, and researchers hope that estrogen can also help prevent dementia in those with Parkinson's disease. But estrogen is a powerful hormone; although many women take it to mitigate the effects of menopause, it is implicated in promoting certain cancers of the reproductive system. Until clinical trials better establish the ratio of risk to reward, Mayeux doesn't recommend taking estrogen solely to protect against Alzheimer's.

Scientists are eager to devise drugs that imitate estrogen's positive role in cognition without subjecting women to an increased risk of cancer. Estrogen may stave off Alzheimer's disease by directly influencing nerve cells in the brain. Researchers hope to find chemical substitutes that affect only these cells. Such drugs might benefit men, too: males produce estrogen from testosterone, and testosterone levels wane with age. The right estrogen might delay Alzheimer's in men without subjecting them to the feminizing effects of traditional hormone therapy.

Other promising leads come from studies of identical twins. In the early

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coping with alzheimer's

Talk of an eventual cure for Alzheimer's generates a lot of excitement, but millions of people must deal with the devastation of the disease right now. Much depends on creative coping.

Barry Reisberg of New York University has studied the course of Alzheimer's for more than two decades. He argues that the characteristic decline can be understood best as a reversal of childhood development. The sufferer incrementally loses the ability to handle finances, then to dress, then to be continent, speak, walk and sit up.

This view must be handled with caution, so that the adults are not infantilized. But it may be useful in guiding caregivers. "A [late-stage] Alzheimer's patient requires the same amount of care as an infant," Reisberg says, and he doesn't mean just feeding and bathing. "You would read to an infant; you should be reading to the [late-stage] Alzheimer's patient, too." What the Alzheimer's sufferer needs most is attention and activity. Simple exercise reduces agitation. Visiting them when they get restless at night calms them.

About two thirds of Alzheimer's patients are cared for at home by family, according to Peter Rabins of the Johns Hopkins University School of Medicine. This can be tough. The founding of the Alzheimer's Association in 1979 focused resources to help those family members, he says. What the families need is practical assistance: an aide to help with bathing, day care so the breadwinner can work, and emotional support.

Teaching families specific coping strategies can alleviate depression—among patients and caregivers alike. "Oftentimes it's just become this stressful, difficult situation," says Linda Teri of the University of Washington. "The patients can't do things they used to enjoy, they get frustrated, and the caregivers may not understand what they still like to do."

One important focus is identifying appropriate pastimes. The family members of one former professor with Alzheimer's discovered a pleasant, stimulating activity after recalling how he loved doing the *New York Times* crossword puzzle. They found a variety of children's word puzzles he could still handle. "You give caregivers strategies, ideas," Teri says, "and they come back and say, 'We had a nice day yesterday. We haven't had that in a long time.'" —*M.S.*

NEW DAY: Patients with advanced disease relearn basic skills at the Maria Wolff Alzheimer's center in Madrid.

MARIA WOLFF ALZHEIMER'S CENTER

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1980s John Breitner, now at the Johns Hopkins School of Public Health, helped to show that Alzheimer's disease aggregates in families: "If you could follow hypothetical relatives of somebody with the disease, let's say siblings, out to age 90 or 95, then almost half those siblings would themselves get the disease—a much higher rate than in the general population." To tease out how much of this aggregation is a result of genetic inheritance, rather than shared family environment, several groups studied the occurrence of Alzheimer's in identical and fraternal twins. The studies suggest that one half to three fourths of a person's disposition to Alzheimer's is inherited. But that leaves plenty of room for outside influences.

At Duke University, Breitner and his colleague Brenda Plassman focused on twin pairs in which only one twin had Alzheimer's. The disease often develops in the initially unaffected twin after a lag, but in some identical pairs the second twin remains free of disease for 20 years after it appears in the first, in one case almost two decades. The researchers studied the histories, lifestyles, infirmities and medications of many pairs. "What surprised us," Breitner says, "was an unexpected association between use of anti-inflammatory drugs and the absence of disease in the unaffected twin."

Many studies have since suggested that nonsteroidal anti-inflammatory drugs, such as ibuprofen, are associated with a reduced risk of Alzheimer's, but other results have been contradictory. The jury is also out on other substances proposed as neuroprotective, including very high doses of vitamin E, until more studies are completed. The wait for definitive answers shouldn't be long. Several trials sponsored by the National Institutes of Health or pharmaceutical companies are already under way, testing anti-inflammatories and vitamin E in hundreds of subjects with mild cognitive impairment. A group led by Breitner at Johns Hopkins is seeking over 2,600 older persons with a family history of Alzheimer's-like dementia for a randomized prevention trial that could nail down the role of anti-inflammatories.

Markesbery advocates a regimen including high doses of vitamin E, C and folic acid, plus nonsteroidal anti-inflammatories for those at highest risk of Alzheimer's—people whose close relatives have the disease, for example. But physician supervision is required; some of these compounds thin the blood and can cause gastrointestinal bleeding. "Right now we're not recommending it for those who don't have the risk factors," Markesbery notes. Eric B. Larson, a longtime Alzheimer's researcher at the University of Washington Medical Center, says, "In my own practice, I don't recommend taking any drug for the principal purpose of preventing cognitive decline. There's nothing out there that's convincing enough."

Greater insight may come from understanding the mechanisms underlying Alzheimer's disease. There are many competing theories. One of the strongest—and the one most drug companies are pursuing—is that the primary villain is a protein fragment called Aß (A-beta) that clumps into plaques in Alzheimer's-affected brains. Aß results when a ubiquitous protein called amyloid is snipped to pieces by two enzymes called proteases. Aß is present in everyone, although no one is sure what it does. But when disposal of Aß can't keep up with its production, trouble may loom. Various genetic mutations that cause rare early-onset Alzheimer's increase the production of Aß, whereas two other genes altered in late-onset disease may be important for clearing Aß.

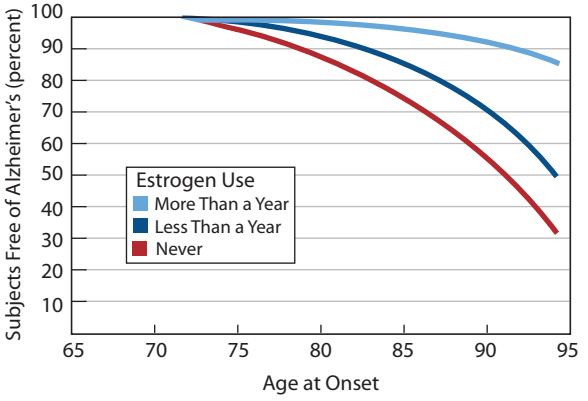
Anti-inflammatory drugs may reduce risk of the disease.

Protease-inhibiting drugs are in the works at several pharmaceutical companies, in hopes that simply cutting back Aß production will prevent Alzheimer's. "Drugs are about to enter clinical trials. They really exist, and they reverse plaque lesions in mice," reports Dennis Selkoe of Harvard Medical School, who has been hunting down Aß for years. Similar medicines have met with great success in the past, including the protease inhibitors that have recently revolutionized HIV treatment. But even if the new drugs block Aß overload and plaque formation, it remains to be proved whether that's enough to beat Alzheimer's. And there are always worries about side effects.

Another promising approach is vaccination to spur the body's own immune system to clear Aß. Mice that overproduce Aß develop Alzheimer's-like plaques as they age; immunization with Aß not only prevents the appearance of such plaques in young mice but reduces the extent of existing plaques in older ani-

delaying alzheimer's

with estrogen



AFTEREFFECT: In a Columbia University study, women who had taken estrogen for postmenopausal treatment also postponed the onset of Alzheimer's.

LAURIE GRACE

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mals. Human clinical trials are now under way at Elan Pharmaceuticals, a firm in South San Francisco that Selkoe helped to start in the 1980s. "Drug companies are working 24 hours a day, and so am I," he explains. "My wife says, 'Why don't you get going—you're going to get the disease before you cure it.' I don't want that to happen."

Calming the Parkinson's Storm

Stronger signs of hope for fighting neurodegenerative disorders may be found in the history of treatment for Parkinson's disease, which strikes at age 60 on average. With no reliable treatment decades ago, its onset often meant a quick decline to years of crippling tremors and rigidity. There has since been some success with a drug called levodopa. The first whisper of tremor or a slightly odd gait means that a Parkinson's sufferer has already lost 70 or 80 percent of a tiny segment of the brain that churns out the signaling chemical dopamine. Without dopamine, neurons that control motor activities go haywire, leading to shaking, slowness and rigidity. As more and more dopamine-producing neurons die, sufferers can develop balance problems, crippling distortions of the hands and feet, and episodes of freezing in midstep. Late-stage Parkinson's often means confinement to bed and wheelchair.

Levodopa can't halt the progress of the disease, but it can replace missing dopamine, with miraculous effect. Many of those afflicted with Parkinson's are symptom-free after their first dose. Doctors started relying on the drug in the late 1960s, and today it is almost universally prescribed. "Levodopa was really one of the great biological successes of the century," says C. Warren Olanow of Mount Sinai.

SILENT SHOCK: Electrodes inserted deep into the brain deliver current from a battery implanted near the collarbone to quiet misfiring neurons that cause severe Parkinson's disease.

MICHEL F. LÉVESQUE *Cedars-Sinai Medical Center*

Like most classic heroes, though, levodopa has a dark side. At first, its benefits last hours on end, but after five or 10 years many patients take levodopa much more frequently and still can't get a consistent effect. "You could be in a grocery store, reaching into your purse to pay, and all of a sudden you go 'off'—you can't move, and you don't know when you're going to come 'on' again," says neurologist Jerrold Vitek of Emory University. "One patient told me about being bent over his couch to pick something up, and he froze like that for two hours." Many people also develop involuntary motions in response to the drug.

The new challenge of Parkinson's treatment is to smooth out levodopa's effect or retire the chemical altogether. One long-standing strategy is pairing levodopa with other drugs. Some compounds ensure a richer stream of levodopa to the brain. Others act to delay temporarily the onset of levodopa therapy as long as possible. Then there is brain surgery. It turns out that certain neurons that go awry in Parkinson's are actually hyperactive; by burning a tiny hole in specific brain regions, surgeons can quell tremor and alleviate rigidity to various degrees.

But the burning may not solve all problems, and it destroys brain cells, perhaps healthy ones needed for other functions. More and more, surgeons are switching to deep brain stimulation (DBS). In this technique, an electrode inserted deep into the brain and powered by a battery implanted near the collarbone silences neurons that would otherwise misfire.

DBS can turn some patients' lives around. Before the new surgery in 1998, Vern Setterholm's Parkinson's disease had advanced to such a degree that he had trouble handling silverware, dressing himself, even shaping his face into a smile. Now the tremor in the 81-year-old retired executive's right hand is gone, he can grin, and he enjoys exercise class a few times a week. Asked whether he'd have this new kind of brain surgery again, Setterholm shoots back, "If they wanted me tomorrow, I'd be there."

Olanow says he has patients who are "totally unable to be controlled with medicine. They are frozen, cannot move. We turn on the stimulator, and they get up and start walking. It's absolutely amazing."

The use of DBS to control Parkinson's symptoms was pioneered in France. Although still experimental, using DBS in the thalamus and other brain structures to ameliorate crippling rigidity is becoming more popular. One great payoff: DBS often reduces the side effects of levodopa, which can then continue

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to be used to manage the disease. Steven Gaede of St. John Medical Center in Tulsa, one of the first Americans to perform the procedure, figures that about 1,000 DBS operations were done in the U.S. last year.

Currently DBS is used for advanced Parkinson's patients, those "at the end of the rope," Vitek says. There's talk of starting much earlier, to slow Parkinson's before its effects become extreme. Ethical questions abound, though; the risk of major complications is 3 to 5 percent, and the benefits of early use are still highly speculative.

The next dream is replacing the dopamine-producing neurons that die in Parkinson's. In one experimental approach tried at several research centers, surgeons transplanted human fetal neurons that produce dopamine into the brains of Parkinson's patients, hoping to restore some normal dopamine manufacture. They've achieved modest success so far. Ideally, the transplanted cells would come from the patients themselves. This notion was outlandish just a few years ago, before scientists proved that even adult human brains generate new neurons from precursors known as stem cells. Gage of the Salk Institute says of his experimental work with animals, "We and others have shown that if you take primitive cells from a lab culture, you can actually put them into parts of the brain that are damaged, and they can turn into cells that are appropriate for whatever is happening in that part of the brain."

Physicians are eager to harness this astonishing potential. Already neurosurgeon Michel F. Lévesque of the Cedars-Sinai Medical Center in Los Angeles has launched the first clinical trial using patients' own cells for transplant. From a snippet of brain taken during surgery, he says, "we are able to identify about 10 to 15 neural stem cells on average." Properly fed, these cells multiply into the millions over four to six months and are coaxed into becoming dopamine-producing neurons that can be placed back in the patient's own brain. Levesque has performed one such transplant so far and expects to do 12 more, but it's far too early to judge the results.

Perhaps the only breakthrough more exciting than giving people a shiny new set of dopamine-producing neurons would be helping them keep the originals. But no one knows what causes Parkinson's disease. The idea of a toxin is intriguing. In the 1980s drug addicts who shot up with a relative of morphine resembling a pesticide came down with the classic symptoms of Parkinson's. Vitek says that although some patients seem to be genetically predisposed to acquire the disease, it's also possible that "exposure to an environmental insult gets the ball rolling." The details remain a mystery.

Researchers are busy testing hundreds of drugs, hoping to toss a molecular monkey wrench into whatever process kills the neurons. The most promising clinical trial began in the late 1980s and involved 800 early-stage Parkinson's patients at 28 research centers. The patients given a drug called selegiline delayed levodopa therapy about nine months longer than those on a placebo. It's not clear how much of the effect was a result of preventing the disease's spread, rather than relieving its symptoms. (The brains weren't dissected because the patients still needed them.) "But there is no question that selegiline slowed the appearance of disability in Parkinson's patients," says Olanow, who sat on the study's steering committee. Whether for treatment or prevention, that's good news.

KAMENKO PAJIC *AP Photo*

VISIBILITY: Awareness of Parkinson's has been raised by public figures, such as U.S. Attorney General Janet Reno, who have disclosed they are battling the disease.

Mia Schmiedeskamp *holds a Ph.D. in biochemistry and contributes regularly to* Scientific American Presents.

Further Information

Alzheimer's Disease: A Guide for Families. Lenore S. Powell and Katie Courtice. Perseus Press, 1993.

The Alzheimer's Association outlines strategies for coping and has details of treatment at www.alz.org on the World Wide Web. By telephone, call 800-272-3900.

The American Parkinson's Disease Association offers information on treatment and helping patients at www.apdaparkinson.com on the World Wide Web. By telephone, call 800-223-2732.

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stopping C

EARLY INTERVENTION MAY PREVENT CANCER FROM BECOMING INEVITABLE WITH AGE

HERCULEAN TASK: Fighting cancer can be like trying to kill the Hydra, which grew back two heads when one was severed.

GIOVANNI CASELLI, REPRINTED BY PERMISSION OF EUROBOOK LTD.

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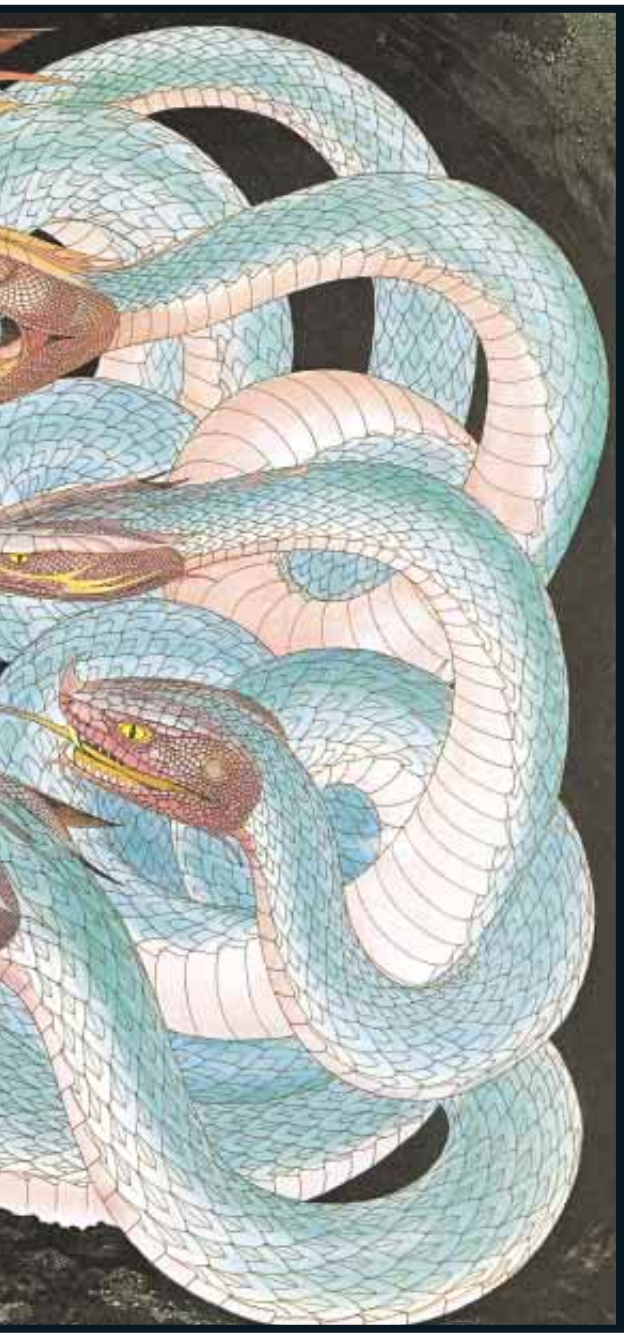
ancer before it starts



BY KEN HOWARD

To a degree, we are all ticking time bombs. As we eat, sleep, think and work, our cells divide again and again. Randomly over time, occasional bad copies are created. Meanwhile external insults such as tobacco smoke trigger other mutations. Most of the sinister cells are too crippled to survive, but some do. And sometimes they undergo further aberrations. When enough mutations have occurred, the result can be cancer.

"We are all walking around with millions of premalignant cells," explains Robert A. Weinberg, professor of biology at the Massachusetts Institute of Technology's Whitehead Institute. "If we live long enough, we'll all come down with one form of cancer or another."

After decades of research, scientists are getting a more complete picture of cancer. Most cancers do not suddenly spring up and run wild. They develop over many years, as a result of biochemical and genetic changes that push healthy cells into a precancerous state and later into cancer. This greater understanding is now prompting researchers to find drugs that can intervene early in the process, rather than be resigned to battling cells that have already become malignant.

In the short term, this "chemoprevention" strategy will probably involve chemical compounds that retard the proliferation of cancer cells in patients who have had cancer surgery, chemotherapy or radiation, buying them more years of life. In the longer term, it is hoped that these agents can slow, stop or even reverse precancerous cells from developing into the full-blown disease. Ultimately, drugs would prevent normal cells from even starting down the path to malignancy.

At the same time, researchers are trying to develop cellular imaging tests that would indicate mutations early in the precancer stage, giving far more advance notice of potential trouble than do current screening tests such as PSAs, which indicate the likelihood of prostate cancer. If such early indicators proved reliable, they could be used throughout life, and at the first signs of trouble a chemoprevention strategy could be set in motion.

Because the road to cancer often takes place over 20 years or more, it is a disease skewed toward old age. Cancer is rare among children. The median age of a U.S. cancer patient is 70, according to the National Cancer Institute. The odds of getting cancer after age 60 are 16 times greater than before age 40, according to the National Cancer Institute.

Although we all carry around mutated cells, it fortunately takes a number of mutations acting in concert to create problems. Michael B. Sporn, professor of pharmacology and medicine at Dartmouth Medical School,

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the progression toward cancerous cells

Cells don't "switch" from normal to cancerous. Over time, biochemical and genetic changes may cause cells to advance gradually in a process of carcinogenesis from normal

TOMO NARASHIMA

suggests we think of our body "as a knit sweater with 100 fibers going along the *x* axis and 100 fibers along the *y* axis. If you have one tear, you still have a functional sweater. But if you get enough tears, it's no longer a functional unit. The nature of carcinogenesis is one of increasing disorganization."

The number of tears any individual sustains in a lifetime depends on an overwhelming number of variables, from inherited genes to diet, environment and lifestyle. But the time lag between the early stages of the process that leads to cancer, called carcinogenesis, and full-blown cancer gives scientists a window of opportunity to stop or at least slow the process before cancer emerges. Recent trials indicate that certain chemicals can indeed interrupt the steady progression from normal to carcinogenic cells.

Don't Wait

Cancer chemoprevention research is 10 to 15 years behind cancer treatment research, but the field is evolving, says David S. Alberts, director for cancer prevention at the Arizona Cancer Center in Tucson. "We have a lot of work to do, but it makes more sense to treat precancerous lesions than to wait for people to develop cancer."

The idea of prevention was demonstrated in practice in 1998, when a historic study with a drug called tamoxifen demonstrated that agents could be introduced into patients to prevent cancer from occurring. The Breast Cancer Prevention Trial (BCPT) of 13,388 women at increased risk for breast cancer showed a 49 percent reduction in breast cancer risk for women taking tamoxifen versus a placebo. The result was so dramatic that researchers identified those subjects taking the placebo before the trial ended, so they could begin taking the drug.

"The study proves for the first time that you can decrease women's chances of getting breast cancer by taking a pill," says Therese B. Bevers, medical director of the M. D. Anderson Cancer Prevention Center in Houston. Soon after the results were announced, the Food and Drug Administration approved tamoxifen as the first drug that can be prescribed to reduce the risk of a cancer.

Tamoxifen is far from perfect, however. The trial linked it with an increased risk for endometrial cancer and pulmonary embolisms. Over the next 10 years, tamoxifen will be compared with another drug, raloxifene, which is used for treating osteoporosis. During an osteoporosis trial, it was observed that women on raloxifene had a 76 percent decrease in risk for invasive breast cancer, but there was no corresponding increase in risk for endometrial cancer. The Study of Tamoxifen and Raloxifene (STAR) has already begun to enroll 22,000 postmenopausal women and will follow their progress over five years.

The trial may offer clinical corroboration in humans of cancer prevention seen in animal studies. Tamoxifen and raloxifene are known as selective estrogen receptor modulators (SERMs)—chemicals that block estrogen reception in some tissues while mimicking the hormone's effect in others. Animal studies have shown that the use of two SERM agents with different mechanisms of action—in these cases, fenretinide and tamoxifen—can suppress cells' advancement from precancer to cancer.

Developing a Preventive Arsenal

Discovering a prevention pill for any one cancer will nonetheless prove difficult. In breast cancer, for instance, a variety of mechanisms are implicated, and there are various types of breast cancer that respond differently to hormones such as estrogen. "Cancer is not one disease but hundreds of diseases," emphasizes Steven K. Clinton, program leader for cancer prevention and control at the Ohio State University Comprehensive Cancer Center.

Many cancers, however, harm similar tissues in the body, such as the epithelial tissue that lines all internal organs. "Over half of cancer deaths in adults are epithelial, including cancers of the lung, breast, prostate and colon," says Dartmouth's Sporn. "From what we know, you have to have a lot of mutations—a series of multiple hits—to lead to cancer." Because the hits accumulate with age, intervening early could prevent our cellular sweater from sustaining too many tears as we get older and older.

The approach, then, in designing drugs to thwart carcinogenesis is to take aim at various points in the process where mutations may occur. One target is drugs that limit the damage from substances that can cause cell mutations, such as tobacco smoke, environmental pollutants

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to precancerous to cancerous. Today's treatments attack only the last stages. The goal is to detect this growth earlier and intervene.

Invasive carcinoma **Metastasis**

and anything toxic we may eat—from nitrosamines in bacon to pesticide residue in fruits and vegetables. Another target is to stop random genetic miscopies from going further down the road toward cancer. A third target is to intercept "free radicals"—errant oxygen molecules released during normal cellular metabolism that can damage cells and possibly trigger genetic mutations. Antioxidants currently under study include selenium, beta-carotene and vitamin E.

Some unusual cases of cancer may provide opportunities to test the chemoprevention strategy. For example, people with the inherited disease familial adenomatous polyposis (FAP)—about 1 percent of colon cancer patients—are at very high risk for colon cancer. They are born with a mutation in their *Apc* gene, a tumor-suppressant gene whose main job is to prevent cancer cells from multiplying uncontrollably. It leads to "lots of polyps in the colon, and 100 percent of the patients then develop colorectal cancer at a young age," explains Waun Ki Hong, professor of medicine at the M. D. Anderson Cancer Center. The current standard of care is prophylactic removal of the colon. But recent understanding of the carcinogenesis of colon cancer indicates possible additional forms of treatment. Preliminary data suggest that two anti-inflammatory drugs, sulindac and celecoxib (Celebrex), may reduce the number of polyps in FAP patients enrolled in clinical trials. But the long-term efficacy is uncertain. Clinical trial data on sulindac indicate that polyps regress while such drugs are administered but may recur afterward, according to Robert J. Mayer, director of the center for gastrointestinal oncology at the Dana-Farber Cancer Institute in Boston.

It is still unknown whether Celebrex would reduce cancer in the general population, and even if it did, the drug may have potentially adverse side effects, perhaps on other organs. Investigators have already begun to look at a broader group of patients, those with sporadic adenoma polyps, of whom 30 percent will have additional polyps after three years. If the drug is deemed beneficial and safe after a three-year trial, researchers might move to larger populations at less of a risk.

Future Prevention Trials

The design of trials for larger populations will be aided by better understanding of specific carcinogenesis pathways. Work on the Human Genome Project may contribute through the identification of genes that may fos-

reduce your risk of cancer

Most cancers stem from an accumulation of genetic faults and exposure to environmental hazards and carcinogens over time. Preventive strategies, such as not smoking and good diet, can reduce cancer risk, but don't be lured by fads or pills that can purportedly "prevent" or "cure" cancer. "There are a lot of people who promote substances in health food stores and supermarkets," says Steven K. Clinton, program leader for cancer prevention and control at the Ohio State University Comprehensive Cancer Center. "These people are entrepreneurs and not scientists. They are selling $50 bags of garbage."

For those of us who'd like to do something reputable to perhaps increase our odds of escaping cancer, here is the accepted medical wisdom, according to "7 Ways to Prevent Cancer," by the Harvard Center for Cancer Prevention at the Harvard School of Public Health.

You can further improve your cancer defenses by knowing your family's history of cancer and getting recommended screening tests at appropriate ages [*see box on next page*].

1. Eat a healthy diet. Make fruits and vegetables part of every meal. Opt for chicken, fish or beans instead of red meat. Choose foods like pasta, brown rice and whole wheat bread. *Lowers risk of cancers of the prostate, breast, lung, colon, rectum, stomach and pancreas.*

2. Get at least 30 minutes of physical activity every day. Many activities count: walking, jogging, dancing. Any activity is better than none. *Lowers risk of colon cancer and may lower risk of breast cancer.*

3. Drink no more than one alcoholic drink a day. One drink is a glass of wine, a bottle of beer or a shot of liquor. *Lowers risk of cancers of the breast, colon, rectum, mouth, throat and esophagus.*

4. Maintain a healthy weight. *Lowers risk of cancers of the colon, rectum, uterus and breast.*

5. Don't smoke. This includes cigarettes, pipes, cigars and chewing tobacco. *Lowers risk of cancers of the lung, throat, pancreas, kidney, bladder, cervix, prostate, colon and rectum.*

6. Protect yourself from sunburn. Stay out of direct sunlight between 10 A.M. and 4 P.M., the peak burning hours. Use hats, long-sleeved shirts, and sunscreens rated SPF 15 or higher. Do not use sunlamps or tanning booths. *Lowers risk of skin cancer.*

7. Follow safe sex practices. *Some sexually transmitted infections are linked to cancers of the cervix, vagina, anus and liver.* —*K.H.*

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early cancer detection

The American Cancer Society recommends the following tests to maximize early detection of cancer, thereby improving the chances for effective treatment.

GENERAL

A cancer-related checkup is recommended every three years for people aged 20 to 40, every year for ages 40 and older. Depending on age, the exam might check for cancers of the thyroid, oral cavity, skin, lymph nodes, testes and ovaries.

BREAST

Women aged 20 to 39 should have a clinical breast exam (CBE) every three years. Women aged 40 and older should have an annual mammogram and an annual CBE. All women should perform monthly breast self-examination.

COLON AND RECTUM

Beginning at age 50, men and women should follow one of the schedules below:

- Fecal occult blood test every year and a flexible sigmoidoscopy every five years.
- Colonoscopy every 10 years.
- Double-contrast barium enema every five to 10 years.

A digital rectal exam should be done at the same time as sigmoidoscopy, colonoscopy or barium enema.

PROSTATE

Beginning at age 50, men with a life expectancy of at least 10 years should have an annual prostate-specific antigen (PSA) blood test and a digital rectal exam. Men in high-risk groups (two or more affected first-degree relatives) and black men should begin at a younger age, such as 45.

UTERUS

Cervix: All women aged 18 and older (or younger if sexually active) should have an annual Pap test and pelvic exam. After three or more consecutive successful results, the Pap test can be performed less frequently, after discussion with a doctor.
Endometrium: Women at high risk of uterine cancer should have a sample of endometrial tissue examined when menopause begins.

SOURCE: "Cancer Facts & Figures 2000," American Cancer Society

ter initiation of tumors. Epidemiological studies may also uncover precancerous associations. One example is the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), begun in 1985 by the National Cancer Institute. The trial failed to demonstrate that beta-carotene prevented lung cancer for the Finnish smokers enrolled, but analysis did show that the men in the vitamin E (alpha-tocopherol) arm of the study experienced 34 percent fewer cases of prostate cancer and 16 percent fewer cases of colorectal cancer.

Discovery of biomarkers that are associated with precancerous lesions could also become an important tool in prevention studies. Myriad markers have been proposed, but none have yet been validated. "We have nothing like LDL [the bad cholesterol] levels that are linked to heart disease," says Peter Greenwald, director of the division of cancer prevention at the National Cancer Institute. Finding a marker would improve research efficiency and save money. The markers would also provide a basis for evaluation of the general population for risk factors, helping doctors decide who might be a candidate for a particular chemopreventive agent.

Other technologies to evaluate risk factors are also being developed. Currently there are only a few screening tests (such as the Pap smear for uterine cancer) that are able to detect precancerous cells, allowing intervention before progression to fully expressed cancer. If more tests were developed, it would still be difficult to access organs such as the prostate, liver or breast as easily as the cervix to get cell samples. And doctors can't biopsy the entire population. Even if they could, the results wouldn't support the effort: the likelihood of actually hitting the specific spot in an organ where cancer may be developing would be too small.

The grand solution would be the equivalent of x-rays on the gene level, so that an entire organ could be evaluated noninvasively. Unlike traditional medical imaging, which is based on macroscopic information such as bone mass and blood flow, this "molecular imaging" could peer into cells at the microscopic gene level, explains Ralph Weissleder, director of the Center for Molecular Imaging Research at Massachusetts General Hospital. Researchers must understand more about molecular changes in precancerous cells, however, before imaging schemes can be devised. Weissleder estimates that practical use of this tool "is decades away."

What should people do until better imaging technology, biomarkers and preventive drugs arrive? Wait for more data from the dozens of chemoprevention trials being supported by the National Cancer Institute. And keep eating your fruits and vegetables.

KEN HOWARD, *a journalist based in New York City, is making sure that he eats plenty of grapefruit and carrots.*

Further Information

Prevention of Cancer in the Next Millennium. Report of the Chemoprevention Working Group to the American Association for Cancer Research in *Cancer Research,* Vol. 59, pages 4743–4758; October 1, 1999. (For reprints, call 215-440-9300.)

Harvard Center for Cancer Prevention (www.hsph.harvard.edu/cancer).

National Cancer Institute's CancerNet (http://cancernet.nci.nih.gov/).

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BETTER UNDERSTANDING OF ATHEROSCLEROSIS—THE INFLAMMATION AND BUILDUP OF FATTY DEPOSITS IN BLOOD VESSELS—HAS TRIGGERED NEW APPROACHES TO TREATING THE NATION'S LEADING CAUSE OF DEATH

saving hearts that grow old

BY DELIA K. CABE

BAD BUGS: Common bacteria—*Chlamydia pneumoniae* (*left*), *Helicobacter pylori* (*right*) and other microorganisms—may cause infections that lead to heart disease.

A. B. DOWSETT SPL/Photo Researchers, Inc. (left); KARI LOUNATMAA SPL/Photo Researchers, Inc. (right)

Blood vessels are built to last. Up to about 100 years, some experts say, under normal wear and tear. For that to happen, you not only have to abide by a heart-healthy lifestyle—low-fat diet, weight in check, exercise, stress management, blood pressure control, good cholesterol numbers, moderate alcohol use, no smoking—but you also should be a woman, have the right genes and age slowly.

Cut to reality: we're not perfect. Our blood vessels endure various assaults because of factors only some of which we can control. We get heart disease—some 14 million Americans have it, and 500,000 die from heart attacks annually. The older we get, the more likely it is we'll end up with it. The proof is in the numbers: heart disease affects an estimated 15 percent of adults in their late 30s to early 40s, about 50 percent of 55- to 64-year-olds, and 65 percent of those in the next decade. Obviously, many of us slept through Heart Disease Prevention 101.

Yet the heart cognoscenti say only half to three fourths of heart disease cases result from the established risk factors. The

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rest come about from infection and other factors that may promote atherosclerosis, the buildup of fatty deposits in blood vessels. Indeed, current research indicates that all of us are in jeopardy from the leading cause of death in the U.S. "Everyone needs to maintain a healthy lifestyle," says endocrinologist Joanne Manson, chief of the division of preventive medicine at Brigham and Women's Hospital in Boston. "Everyone's at risk."

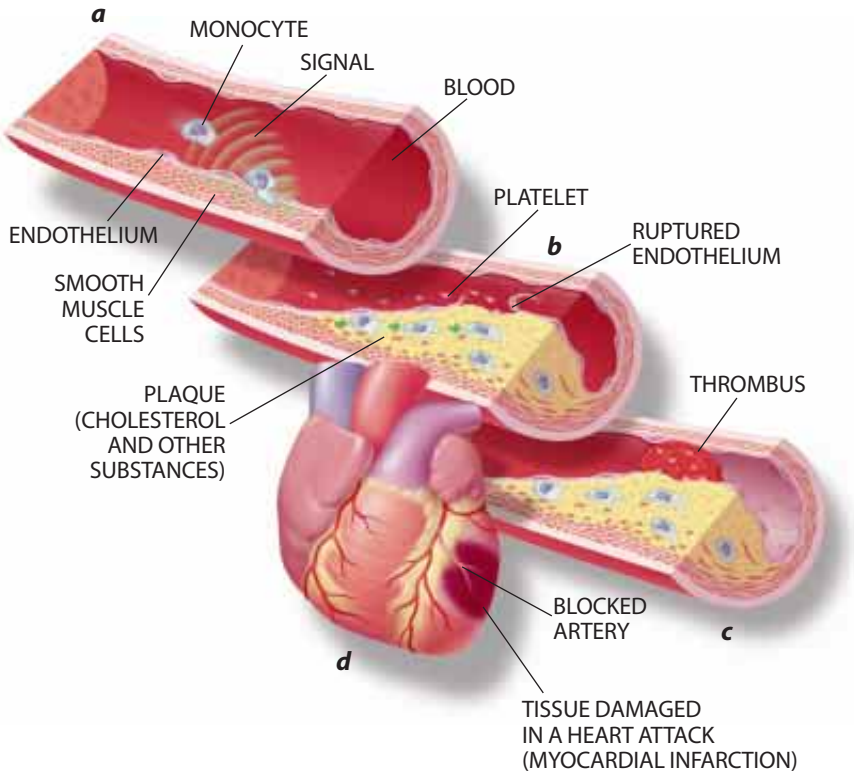
Efforts to find additional means of preventing heart disease have led to the unearthing of about 300 predictors, including bad relatives of the trouble-maker cholesterol as well as bacteria and baldness. Yes, baldness.

Manson and her colleagues at Harvard Medical School, which is affiliated with Brigham and Women's Hospital, published a study this year that found that hair loss, specifically on the crown of the head rather than at the front, is linked to a threefold greater risk of heart disease in men. Blame it on male hormones. The connection may be elevated androgen levels, which are associated with baldness and have been linked to atherosclerosis and a higher risk of blood clotting.

Such a marker as baldness may seem an unlikely place to look for risk factors. But in 1988 Manson's group also found a correlation between height and heart disease. Let's just say that taller people are better off—perhaps because they have wider blood vessels. Such information may help identify people who are more prone to heart disease and may lead to better means for prevention and interruption of disease progression tailored to an individual's physiology. The discovery of many of these markers arose from a closer examination of the cycle of inflammation, plaque formation and injury that causes atherosclerosis, the forerunner to angina and to heart attack and stroke, the major causes of death and disability as we move into later life.

The broadened understanding of the underlying causes of heart disease has paved the way to potential therapies, including antibiotics and ACE (angiotensin converting enzyme) inhibitors. ACE inhibitors were developed to control high blood pressure, but they have recently been found to have therapeutic effects in preventing heart disease.

a primer on vascular disease



OBSTRUCTIONS: The events that precipitate plaque-clogged blood vessels—the disease called atherosclerosis—begin when smooth muscle cells underneath the inner cell lining, the endothelium, release a signal that attracts monocytes (*a*). These white blood cells migrate into and under the endothelium, where they amass cholesterol and other substances. The swollen endothelium may rupture, drawing clot-forming platelets (*b*). The platelets may aggregate red blood cells and form a blood clot, or thrombus (*c*). The narrowed artery may cause chest pain (angina) or, if completely obstructed, a heart attack (*d*).

JOHN W. KARAPELOU

Read My Lipids

Atherosclerosis, which begins in our teenage years and builds up as we age, starts when the smooth muscle cells underneath the endothelium, or inner lining, of blood vessels release a signal in response to high cholesterol levels. This signal attracts monocytes—white blood cells that fight infection and amass cholesterol, calcium and other substances. The resulting cheesy mass, or plaque, bulges like a pimple. Over time, the endothelium loses its elasticity and may rupture. This injury to the lining summons clot-forming platelets, which further restrict blood flow through the already narrowed artery. An inadequate supply of oxygen-rich blood to heart muscle may cause temporary chest pain, or angina, and if blood flow is completely cut off, a heart attack—in clinical terminology, a myocardial infarction. All this from the best-known harbinger of

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heart trouble, the lipid cholesterol. But only to a degree.

Cholesterol has been the cause célèbre in heart disease prevention. Fifty percent of Americans have elevated cholesterol levels. And the increase occurs naturally as we age—mostly after about age 45 for men and age 55 for women. Women in their reproductive years tend to have lower levels than men of the same age. After menopause, their cholesterol levels rise. But we also should fault our lifestyles. Without a doubt, lowering dietary intake of cholesterol and saturated fats does wonders for the heart. The goal is to keep down blood levels of the bad cholesterol (low-density lipoprotein, or LDL), behavior that can produce a 25 to 35 percent reduction in what the pros term "cardiovascular events"—that is, heart attacks, strokes and the like. At the same time, don't forget about raising your levels of good cholesterol (high-density lipoprotein, or HDL), which mops up LDL.

But the picture's more complex. Some people develop heart disease in spite of attaining ideal lipoprotein levels. For them, an approach that goes beyond controlling cholesterol and other lipids may be in their future.

Six years ago researchers with the Framingham Heart Study (the decades-long study that brought us the term "risk factor") identified a relative of LDL called lipoprotein(a) as an independent risk factor for heart disease. Lp(a) fosters the deposition of cholesterol on artery walls and interferes with the body's means of dissolving clots. Lp(a) also enhances oxidation of LDL.

Oxidation is nature's way of spoiling things like food. But old food gets thrown out, whereas oxidized LDL stays in the bloodstream and penetrates the endothelium. Elevated levels of Lp(a), which are most likely genetic, place people in the "high risk" category, as would a total cholesterol level greater than 240 milligrams per deciliter of blood (mg/dl) or an HDL level less than 35 mg/dl. Blood tests to measure Lp(a) have become available, but Lp(a) is difficult to lower. Two therapies that show promise include the vitamin niacin at prescription doses that are 100 times higher than the recommended daily allowance and the hormone estrogen. In addition, a few studies suggest that reduction in LDLs may help.

TAKE TWO ASPIRIN, THESE ANTIBIOTICS, THIS STATIN DRUG, NIACIN, FOLATE, ESTROGEN, AN ANTIOXIDANT SUPPLEMENT, THIS ACE INHIBITOR CALLED RAMIPRIL...
OH, AND DON'T FORGET TO RELAX!
DUSAN PETRICIC

But it now seems that some LDL particles are worse than others. In the few studies done to date, people with predominantly small LDL particles have a risk of heart disease between three and four and a half times greater than those with large LDL particles. Why does size matter? Small particles are more prone to oxidizing, damaging blood vessel walls and invading them 50 percent faster than larger particles to initiate cholesterol accumulation.

Looking for Little Stuff

A blood test to measure LDL particles is useful in determining which drugs would be most effective in individuals with heart disease or in those who have a strong family history of it. Fortunately, current heart disease interventions cut down small-particle LDL levels. These include exercising, taking niacin (but only under a doctor's supervision) or some cholesterol-lowering drugs. Diet can also help lower triglycerides (another type of fat in the blood).

Even the good cholesterol, HDL, turns into a traitor in certain environments, much like a chameleon changes its colors in different surroundings, says cardiologist Alan M. Fogelman, executive chairman of the department of medicine at the University of California at Los Angeles School of Medicine.

Normally, HDL prevents LDL oxidation. But he and other researchers have observed HDL in its other guise. After surgery or during infections, atherosclerotic plaques burst more easily. These ruptures may occur because the immune system has geared up to fight infection. In this environment, HDL changes into a molecule that promotes LDL oxidation. If studies bear out this model, researchers could develop medications to thwart HDL's metamorphosis.

The possibility that the inflammation within the blood vessel walls and the immune system's response might be triggered by an infection led investigators to two bacteria—*Chlamydia pneumoniae* and *Helicobacter pylori* (the latter was recently deemed the culprit in stomach ulcers)—and herpesvirus. Of these three, *C. pneumoniae,* which causes respiratory infections, has received the most attention. The burning question is whether this bacterium, which has been found in 70 to 80 percent of plaques taken from heart disease patients, is an innocent bystander or an accomplice.

Cardiologists Jeffrey L. Anderson and J. Brent Muhlestein of the University of Utah are among several researchers looking for the answer. But these two col-

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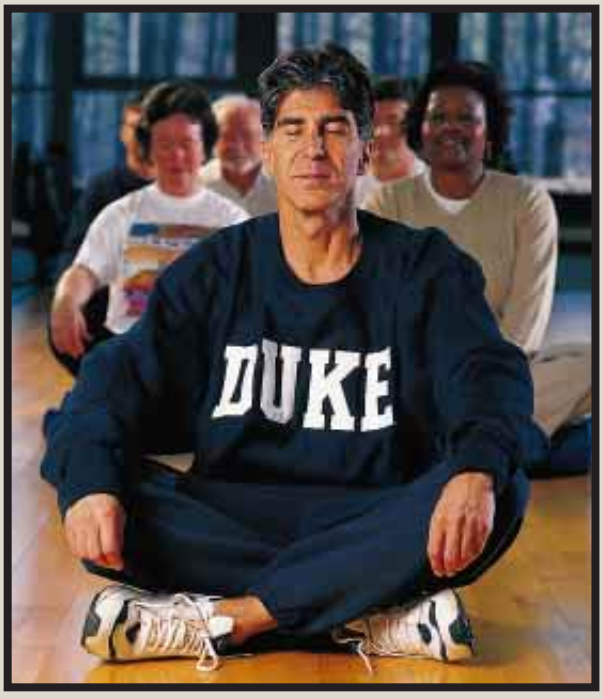
ticked off:
anger can knock you dead

A Barnes and Noble or Borders bookstore carries many of the 1,000 or so stress management guides, primers and tomes all intent on revitalizing, detoxing and streamlining the lives of road ragers and drivers in the fast lane, idiots and dummies, managers and underlings, and a host of others based on the principles of Zen or the habits of zebras. The promise is inner peace and healing, emotional wellness and self-renewal in six seconds, one minute, 16 minutes or a day. Or you could avoid sweating the small stuff altogether.

Why the fervor to calm down? The most important reason can be found in the title of a book, *Anger Kills,* written by psychiatrist Redford B. Williams, one of the pioneers in the research linking heart disease to Type A behavior. Type A people are those who are driven, tense, competitive and hostile, and his work showed that these folks are on the road to cardiac ruin. Stress may age their hearts faster than a New York minute—and it only gets worse as they get older. A study conducted by psychologist James A. Blumenthal of Duke University Medical Center, where Williams is director of behavioral research, found that a group of physicians from the University of North Carolina at Chapel Hill who scored in the upper half of a hostility questionnaire administered at age 25 had a four to five times greater chance than those with lower scores of developing heart disease by the time they were 50.

Williams and others have since sifted through Type A characteristics and found that some of the traits are worse for your health. Overt anger has dire consequences, as Williams writes. One study found that an episode of anger doubles heart attack risk up to two hours later. But no increased risk occurred in people who took aspirin, which prevents the blood clots that could cause a heart attack. Such research hinted at a connection between clotting tendencies and anger.

Now stress researchers are focusing on blood flow to the heart to try to uncover a direct relation between stress and heart disease. Ischemia, a lack of blood flow to the heart caused by narrowed or blocked arteries, may produce transient chest pain called angina and may lead to a heart attack. In the 1990s several studies showed that ischemia can be induced by mental stress in the laboratory and by negative emotions in daily life. Hostility and anger were usually the culprits.



HOT UNDER THE BREAST POCKET: James A. Blumenthal of Duke University Medical Center uses meditation and other techniques to teach students strategies to quell anger and hostility.

LES TODD

Results of the largest study to date to measure the heart's physiological response to stress—which combined blood tests and pressure measurements along with radionuclide angiography to view blood flow through the heart—reached publication in the *Journal of Health Psychology* early this year. Headed by psychologist Mark Ketterer of Henry Ford Hospital in Detroit, the study showed that laboratory-induced stress—especially anger and irritability—in heart disease patients caused ischemia more than half the time. Women, who more readily acknowledge their anger, fared better. Williams's

leagues were not about to take their cue from the scientist who gave himself an ulcer by ingesting *H. pylori*. Instead of hardening their arteries in the name of medicine, Anderson and Muhlestein opted for studies on other animals. They set about infecting rabbits, which normally do not develop atherosclerosis, with *C. pneumoniae*. Plaques did indeed appear, and antibiotics reduced the number of these thickenings.

Having shown cause and effect, the researchers set their sights on humans with heart disease who had evidence of past infection with *C. pneumoniae*. After six months on the antibiotic azithromycin, the human subjects had a modest but significant reduction in key markers of blood vessel inflammation: C-reactive protein, tumor necrosis factor, and the interleukins IL-1 and IL-6, all of which are released by the immune system. At the end of two years, Anderson and his colleagues hope to see at least a 50 percent reduction among those treated with the antibiotic in the frequency of heart attacks, angina, stroke, and procedures such as angioplasty and bypass surgery.

Anderson is among the investigators taking part in long-term trials now under way at several medical institutions with large numbers of human subjects. If antibiotics do significantly reduce the incidence, physicians say this would be a major advance in heart disease treat-

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book is required reading in Ketterer's stress management classes, in hopes that the students recognize these tendencies in themselves.

Blumenthal has also published several studies showing that stress serves as a trigger for ischemia. He has found that stress management graduates experienced fewer ischemic episodes. But getting in touch with one's angry side is a gradual process among heart disease patients in his classes. "It's not as if a lightbulb goes off in their heads," Blumenthal says. In addition to observing other people, his relaxation wannabes learn to recognize the physiological reactions to stress and anger, such as increased heart rate and muscle tension.

Once enlightened, the students learn strategies to deal with their anger and hostility. Altering one's thought patterns is vital. Easily angered people engage in all-or-nothing thinking, producing exaggerated reactions to ordinary life events and taking everything personally. Blumenthal teaches them these ABCs in anger management and illustrates with a familiar situation:

Recognize Antecedents: You are driving, and a car cuts you off.
Assess Your Beliefs: He's out to get me.
Know the Consequences: I feel angry.
Dispute the Thoughts: The person was rude, but it wasn't directed at me.

Notice that there's no E for yelling Epithets. Maybe if those ABCs appear on bumper stickers, road rage will diminish. And those bad drivers won't give you a heart attack. —*D.K.C.*

ment. Heart patients who show these inflammatory markers might be prescribed medication to combat the bacteria. "Until that time, though, I think we shouldn't be giving antibiotics to our patients," Anderson says, because studies are still ongoing.

Meanwhile cardiologists are assessing whether taking folate and other B vitamins might lower heart disease rates. Accumulating evidence from the Physicians Health Study, the Framingham Heart Study and others seems to point to a direct relationship. And homocysteine levels in blood could be the smoking gun. Homocysteine, an amino acid that results from the body's metabolism of food, may contribute to atherosclerosis and increase clotting because it makes platelets stickier. In addition, homocysteine may lessen the flexibility of blood vessels, slowing blood flow. In people such as older adults and postmenopausal women, who typically have high levels of homocysteine in their blood, the risk of heart attack and stroke increases. Folate and other B vitamins may bring about a decrease in heart disease risk because they break down homocysteine.

Folate in Your Diet

Randomized, controlled trials are needed to determine if managing homocysteine levels, as is done with cholesterol, could join the list of heart safeguards. Nevertheless, the American Heart Association currently advocates that people who are at high risk for heart disease include more folate and other B vitamins in their diet—at least 400 micrograms' worth. That deed is accomplished simply by eating a balanced diet that includes the already recommended five daily servings of fruits and vegetables.

High blood pressure, or hypertension, was long ago shown to predispose people to atherosclerosis, heart attack and stroke. Hypertension is indeed an affliction of aging. The number of men and women with high blood pressure rapidly escalates in older age groups. More than 50 percent of Americans over age 65 have high blood pressure. First-line treatment to control hypertension involves a healthy diet, exercise and weight loss. If that fails, physicians prescribe antihypertensives such as ACE inhibitors. Until the 1980s, the presumed and only benefit of ACE inhibitors was the foiling of the body's production of angiotensin, a chemical that constricts arteries, so that blood can flow through vessels easier. But new research indicates that ACE inhibitors do more. So much more that the HOPE study evaluating the effects of the ACE inhibitor ramipril in 9,541 heart disease patients at multiple medical institutions was stopped six months early and its results released last November, before publication, so that study participants receiving a placebo could also reap the drug's benefits.

"We got stunning results—more than we expected," says study chairman and cardiologist Salim Yusuf of McMaster University in Ontario. "It is like the discovery that cholesterol drugs lower risks of heart attacks." The data showed a 22 percent overall reduction of heart attacks, stroke or death from other cardiovascular causes. The benefit was independent of ramipril's small reduction in blood pressure. In fact, most of the participants did not have hypertension when they enrolled in the study. Ramipril, Yusuf adds, may have an important effect within blood vessel walls, but it is unknown if other ACE inhibitors work in a similar fashion. Now physicians can offer one more preventive approach to their patients.

But these pills and other advances are meant for those of us who have flaunted time-tested heart-saving advice or the few who have only their genes to blame for abnormal lipid levels and such. As for waiting for that quick fix, researchers promise none. You can hope and pray. Take it from the grand poohbah of heart health, American Heart Association president Lynn A. Smaha: New research findings hold promise but no certainty of licking heart disease, so "in the meantime, take care of yourself."

Delia K. Cabe *is a freelance writer based in Boston who frequently covers health-related issues.*

Further Information

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The Michigan Electronic Library, a project of the University of Michigan and the Library of Michigan, maintains a **Heart and Cardiovascular System site:** http://mel.org/health/health-disease-heart.html

Research projects on heart disease can be surveyed at the Web site of the **National Heart, Lung and Blood Institute** of the National Institutes of Health: www.nhlbi.nih.gov/

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meditations on

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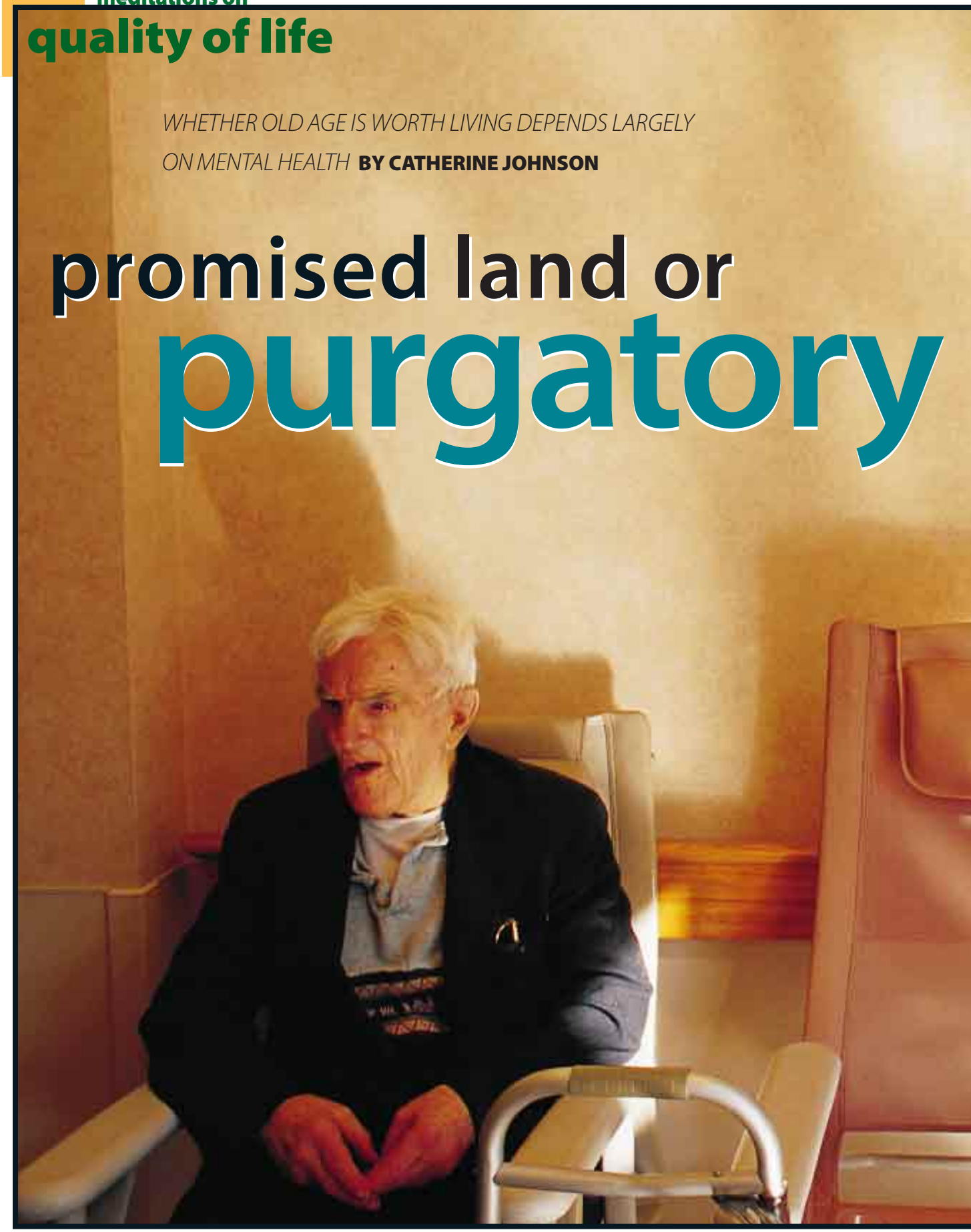
WHETHER OLD AGE IS WORTH LIVING DEPENDS LARGELY ON MENTAL HEALTH **BY CATHERINE JOHNSON**

promised land or purgatory



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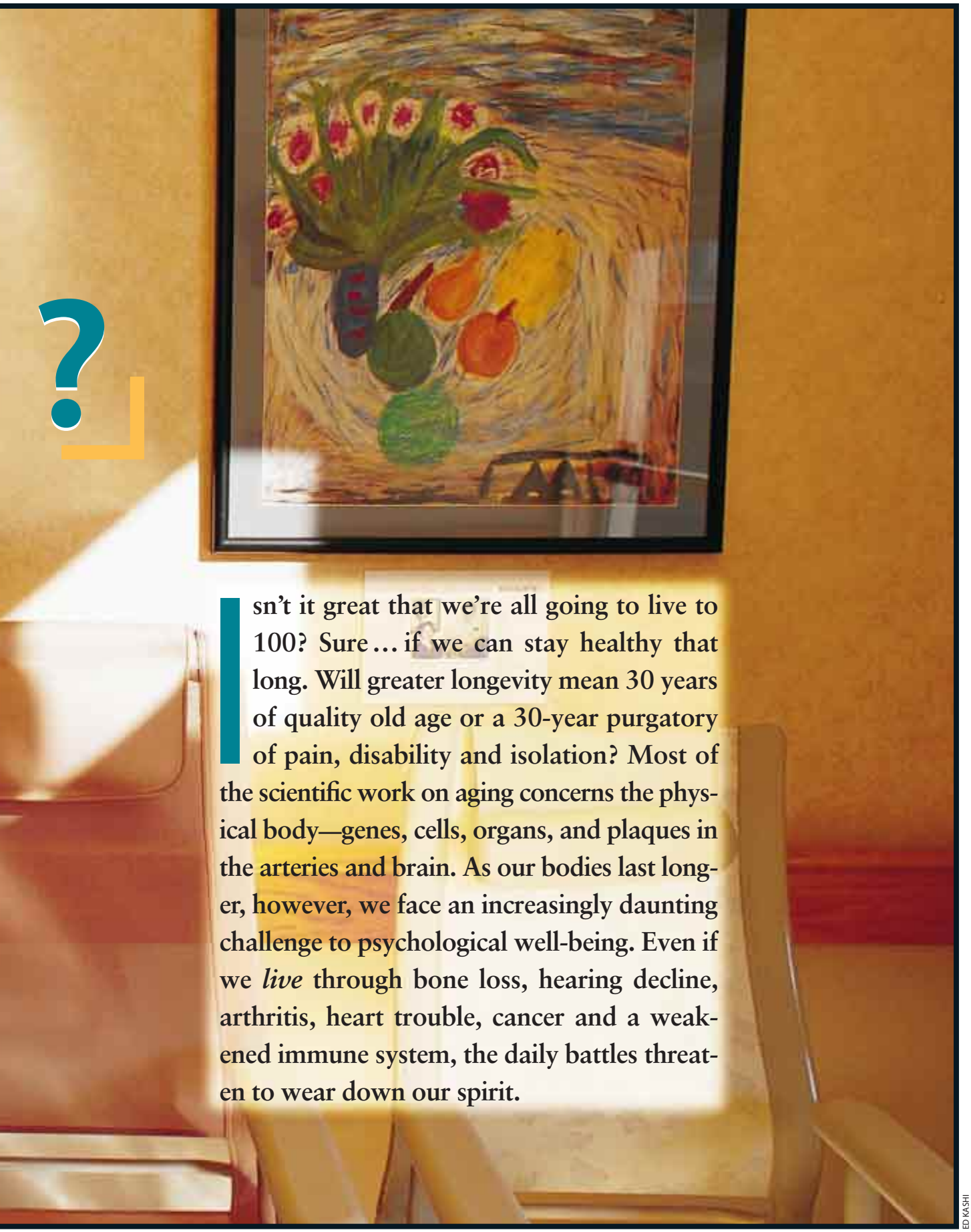

Isn't it great that we're all going to live to 100? Sure… if we can stay healthy that long. Will greater longevity mean 30 years of quality old age or a 30-year purgatory of pain, disability and isolation? Most of the scientific work on aging concerns the physical body—genes, cells, organs, and plaques in the arteries and brain. As our bodies last longer, however, we face an increasingly daunting challenge to psychological well-being. Even if we *live* through bone loss, hearing decline, arthritis, heart trouble, cancer and a weakened immune system, the daily battles threaten to wear down our spirit.

ED KASHI

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Indeed, with a growing arsenal of countermeasures to the physical ailments of aging, quality old age will depend more and more on good mental health. And that's a tough nut to crack, because age weakens our minds as much as our bodies, severely challenging our ability to remain mentally acute and emotionally positive. There is hope, though: science is beginning to provide clues about how to overcome the major mental challenges of old age.

Battling Depression

People are notorious minimizers of unpleasant realities. As University of California at Los Angeles psychologist Shelley E. Taylor and others have shown, "positive illusions" are a standard feature of the psychologically healthy person. On the face of it, there's no reason why people shouldn't simply continue deluding themselves into old age. Many do. When very old and sick people are asked whether they would rather live one year in their current condition or die sooner in good health, they choose quantity over quality.

Still, choosing to live instead of die is a far cry from enjoying a life that is happy or even marginally satisfactory. The truth is, the elderly suffer very high rates of depression compared with the rest of the population. Old age can be a mental grind.

Boston psychiatrist John J. Ratey, author of the forthcoming book *A User's Guide to the Brain*, sees a number of elderly patients in his practice. "Loneliness is a huge issue for them. They don't interact as much. They get a little depressed because they're losing people, structure, function and purpose." Add the physical challenges, and a negative feedback loop begins to spiral. They don't feel like doing *anything* productive, physically *or* mentally. As Ratey observes, "They're losing energy, arousal and vigilance. Going into retirement the large majority of people think, 'Oh, I'm going to have so much time to do stuff,' and then they end up watching TV. Nonaction begets nonaction—these older people don't move enough and slide into lethargy."

A global state of mental and physical torpor is not much of a life. But snapping out of depression by means of self-generated positive illusions gets harder, because with advanced age, positive illusions become difficult to sustain.

No one knows precisely why this is so, but researchers believe that age-related changes in the serotonin system play a key role. Serotonin is the neurotransmitter most closely linked to feelings of happiness, confidence and calm, and it declines with age. Although the neurological basis of emotion is far more complicated than the relative level of one neurotransmitter, researchers nonetheless find that people with low levels of serotonin are more likely to feel depressed, anxious or angry. Car-

the dangers of
overmedication

By the time the average American has turned 70, the seven-day pill organizer may be overflowing with colored capsules. As medicine finds more fixes for the maladies of old age, the elderly are in danger of becoming increasingly dependent on scores of pills, reducing their quality of life and potentially killing themselves via overdose or unintended drug interactions.

The Golden Years are exactly the wrong time to face a panoply of pills. Neither our memories nor our kidneys are up to processing half a dozen different prescriptions half a dozen times a day. It's just too easy to mess up (as this author—a long way from "elderly"—discovered one morning when she took her aging dog's medication instead of her own).

One major cause of the problem is polypharmacy—the prescribing of numerous drugs by different doctors for the same person, often for the same disorder. The marketplace is also implicated. "The elderly obtain drugs from many different sources—over the counter, their local pharmacies, and mail-order sources their insurance companies mandate," notes Joseph J. Bova, owner of Cary's Pharmacy in Dobbs Ferry, N.Y. "They can end up receiving the same medication with different names and not realize they are taking it twice."

CORBIS

CONTRAINDICATION: Too many pills can confuse or harm.

Brian White, a registered nurse at the Community Hospital in Dobbs Ferry, says senior citizens are routinely admitted to the emergency room who are in grave danger from overdoses of necessary medication. And it doesn't even take an overdose to cause serious complications. "As you get older, you don't metabolize drugs as efficiently," White explains, "so medications can build to toxic levels in the blood. Just being dehydrated can cause a dangerously high level."

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olyn Meltzer, associate professor of radiology and psychiatry at the Positron Emission Tomography (PET) Center in Pittsburgh, has found a 55 percent reduction in serotonin receptors in older subjects. (Aging women suffer the further complication of a sharp decline in estrogen after menopause. Estrogen is a precursor to serotonin in the brain.)

Battling depression becomes harder still because the elderly find themselves in the constant company of death. Old people lose friends and loved ones at rates far higher than the rest of us. And when you're 90, you know that your own death is likely to be close.

Reducing Stress

Maybe the most ironic fact concerning the neurology of aging is that while practically every other significant hormone in the body declines precipitously with age, cortisol, the stress hormone, shows no drop-off whatsoever. In fact, old people may show *more* sustained cortisol production when subjected to stress tests. Apparently, we simply cannot exhaust the body's ability to flood itself with cortisol when life gets hairy.

This sounds like some malevolent Greek god's idea of a joke. If so, it gets funnier: the body's ability to *recover* from stress diminishes with age. The stress from a virus, an argument with a friend or a dip in a cold swimming pool stays with you longer when you're old than when you're young. As we age, we get better at becoming stressed and worse at letting stress go.

Lower levels of serotonin combined with higher levels of cortisol make for a harsh cocktail. This is the very hormonal makeup found in clinically depressed young people. Yet researchers are not sure how meaningful this resemblance might be. Owen M. Wolkowitz, professor of psychiatry at the University of California at San Francisco, points out that although the elderly have higher cortisol levels, they are still within normal limits. The real villain might be a drop in DHEA, a hormone that regulates cortisol. "DHEA goes down dramatically with age," Wolkowitz says. "The important thing may be the ratio between DHEA and cortisol." The "grumpy old man" view of the aged takes on new meaning considering the hormonal state elderly men (and women) often endure. If your balance of cortisol is off, those crying children in the supermarket can be *really* irritating.

Here again, negatives beget negatives. A person whose stress response system is permanently stuck on high will develop strategies designed to limit his exposure to stress—strategies that are likely to result in even less involvement with the social world than his fading energy has already decreed.

Stanford University neuroscientist Robert M. Sapolsky observes that when old people are faced with a difficult situation, they are more likely than younger people to distance themselves from it. It may be that the intense stress reaction, accompanied by slow recovery time, makes the cost of a direct approach to life's stressors too great. Withdrawing from society, however, is one of the worst things an elderly person can do; study after study has shown that social support and active engagement with other people combat depression.

Taking Charge

Forcing yourself to fight depression and stress requires initiative and planning. But the single most fundamental change gerontologists see in the normal aging brain is a 5 to 10 percent loss of tissue in the frontal lobes, which are largely responsible for these very skills, notes Mony J. de Leon, professor of psychiatry at the New York University School of Medicine. Although the brain declines slightly in size overall, no other part undergoes a change of this magnitude.

The frontal lobes are the seat of what neuropsychologists call "executive function" (EF), a cognitive capacity defined in the 1990s. Executive function is a person's ability to plan, organize time, stay focused and motivate oneself. Any degree of impairment to EF is going to hamper an elderly person's ability to ward off depression by creating an active, purposeful and structured existence—or even to want to do so. Ratey observes that for all people, a sense of purpose in life—a mission—is essential to happiness as well as to good brain function.

An impaired EF can also interfere with an individual's ability to establish and maintain social support. Motivation to see friends and family may wane. Unattractive personality traits may arise, making others less inclined to spend time with that individual, because another EF function is impulse control. The "grump" was there all along, but it was controlled. Now the older person can no longer manage this behavior.

Stimulants may help counteract brain deficits such as frontal lobe loss. Ratey and his colleagues have begun to treat the loss of energy associated with advanced age with the new medication Provigil, a novel compound that is the first to be approved for narcolepsy in 40 years. No one has pinned down exactly how Provigil affects brain cells, but it has been shown to promote alertness. Ratey describes one patient as "an 86-year-old woman who would have to return to bed for hours each day because

Better drug management strategies are the key to safety. Bova cites the Brown Bag program sponsored by New York State's Pharmacists Society, available at most pharmacies, as one approach. "Patients are asked to bring in the contents of their medicine chests for their pharmacist's review," Bova explains. "We can pick up problems such as duplication of drug therapy and help avoid mistakes." Midwesterners can find local Brown Bag help through the Meijer Online Pharmacy (www.meijer.com/pharmacy/ askpharm_frameset.html).

Ultimately, though, advances in medicine itself will provide the best solution. Researchers anticipate that when the Human Genome Project is completed we'll discover hidden links among disorders we have traditionally viewed as distinct. If, say, we find an underlying genetic link among heart disease, Type II diabetes and high blood pressure, it's possible we'll need only one highly refined medication to treat them all.

Until then, if you're elderly, keep the organizer organized, and if you're not, offer to help someone who is. —*C.J.*

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of tiredness. Now she is 'thrilled' with a restored energy level and sense of well-being. Instead of being slumped over in bed, she is reading, catching up on her correspondence and exercising." Ratey has also found that Provigil can counteract the sedation that often accompanies the many medications taken by seniors. Soon the elderly may routinely be given medications like this to treat frontal-lobe deficits.

Mental Exercise Pays Off

If by now you're becoming depressed and stressed about the prospects for a mentally healthy old age, cheer up. Help may come from sustaining simple daily habits in our lives. The key tactic is to keep challenging the brain.

Although some decline in hormones is inevitable, mental decline is not. One of the most fundamental research findings of the 1990s—"the decade of the brain"—is that neurons and their interconnections can remain remarkably plastic into one's 80s and beyond. The brain is not a preset, unalterable network of cells. Aging connections can remain flexible, and new ones can even be formed, regardless of how old that gray matter becomes. This is extremely important because it indicates that the brain can reroute connections around areas that may be growing rigid with age or even bring those areas back to greater functionality.

"The brain remains plastic until death," says Arnold B. Scheibel, a robust 78-year-old professor of neurobiology and psychiatry at U.C.L.A. and former director of the Brain Research Institute. "With plasticity we can short-circuit evolution. We can force ourselves to evolve within our own lifetimes."

Scientists are only beginning to understand how we can maintain our brain's plasticity, but a few promising avenues have been found. Physical exercise is one. Although the mechanism has not been pinned down, the physical exertion of the cardiovascular and muscular systems seems to keep the brain more pliable. One study shows that aerobic walking improves executive function in people between the ages of 60 and 75, and there is no reason to believe that this would not hold true for 80- and 90-year-olds. The subjects' ability to switch rapidly from one task to another improved, their distractibility decreased, and their ability to *stop* doing whatever they were doing (like taking their foot off the accelerator while driving) increased.

All three of these skills, by the way, are the ones affected in childhood disorders such as attention-deficit hyperactivity disorder. It is easy to see how the notion of old age as a second childhood developed—and how age-related brain deficits may one day be treated in much the same way.

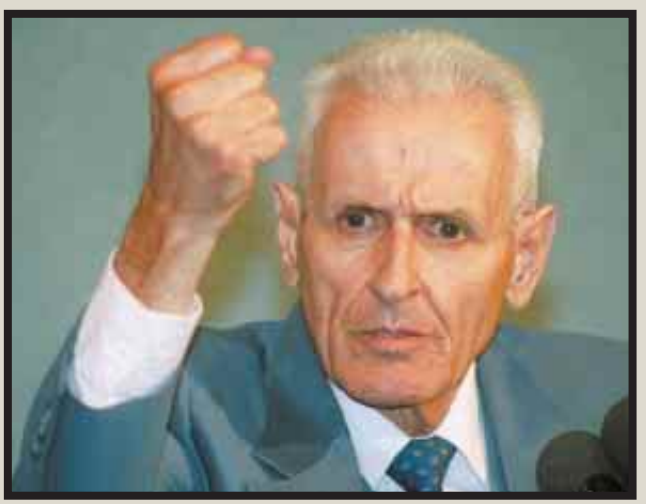
There are reams of evidence that old people who stay in touch with family, friends, church and society stay in better shape physically and mentally. Data even show that an active social life bene-

a right
to die?

Advocates of the right to die—as well as journalists covering the issue—routinely raise the horrors of old age as an argument in favor of assisted suicide, championed by Jack Kevorkian. But oldness, like beauty, is in the eye of the beholder. Although an 80-year-old might look miserable to a middle-ager, she is most likely to compare herself to a 90-year-old—and to conclude that she is doing reasonably well.

This positive outlook is a standard feature of human psychology. Even major illness and loss cannot put a dent in an ordinary person's sense of well-being for more than a few years. In study after study, victims describe themselves as being as happy overall as they were before their trauma.

The trick to happiness may be social contact. Researchers have found that a sick or disabled senior who is surrounded by friends and family will tend to characterize his or her life as satisfactory. Studies by Joel Tsevat of the University of Cincinnati Medical Center found that 43 percent of his subjects in the worst physical condition and 51 percent with severe pain described their quality of life as good. In short, no one can divine an old person's state of mind by looking at the state of his or her body.



WILFREDO LEE *AP Photo*

ASSISTED SUICIDE CRUSADER: Jack Kevorkian.

It is a slippery slope from believing in assisted suicide to simply assuming that a sick old friend or relative wants someone to help him or her die. Older Americans, who have a strong collective voice in politics and culture, should be allowed to speak for themselves. —*C.J.*

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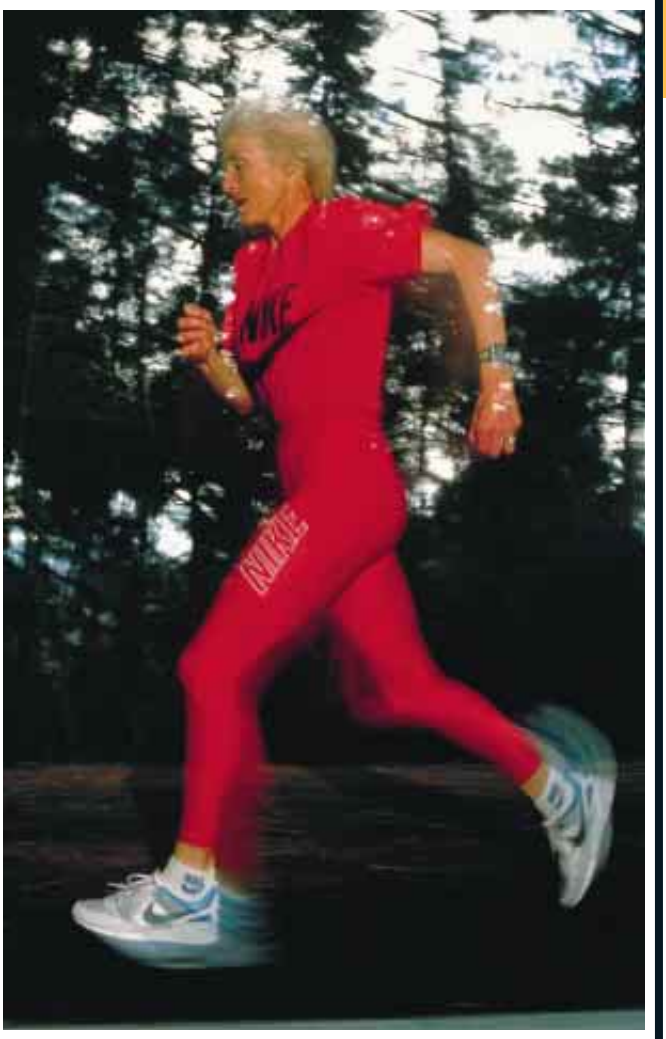
fits brain function as much as physical fitness does. Staying socially active also helps maintain a positive attitude, by improving feelings of self-worth. One study showed that older adults who attended religious services at least once a week had a survival advantage over those who did not attend. Whether it was the activity or a spiritual boost, the message is clear: you've got to stay engaged.

Elderly people who simply cannot get around may find help from the Internet. An aged person who can no longer walk or drive can find great cheer in keeping up with friends and family via exchanging e-mail, electronic photos and on-line chats.

Perhaps the most critical act in maintaining plasticity is mental exercise. As Scheibel points out, mental exercise keeps the brain alive. "We now realize, through some very exhaustive work, that the so-called aging brain is just as powerful in learning as younger brains. The old phrase 'You can't teach an old dog new tricks' is simply not true." Indeed, mental challenges, from crossword puzzles to political debates with friends, keep neuronal connections strong, just as physical exercise keeps muscle fibers strong. The "workout" lesson is the same: use it or lose it.

Undertaking completely new hobbies, vocations, or intellectual pursuits can help even further. Learning in old age may take a little longer, Scheibel says, but we remain potential learners our entire lives.

More exact advice on how to preserve mental health will surely expand as millions of baby boomers gray. The sheer numbers will change everyone's view of what old age can and should be. Robust mental health will be seen as an entitlement, not the minor miracle it is today. As a result, a significant segment of medicine will change. "Geriatrics as a specialty is only 15 or 20 years old—there was such a small clientele until 25 years ago," Scheibel says. "And research interest in aging goes back only another 15 years before that."



USE IT OR LOSE IT: Physical exertion helps to keep the brain supple; mental exercise keeps it sharp.

ED KASHI

At the social level, retirement will change substantially or be done away with altogether. Scheibel himself exemplifies the trend: forced retirement has been abolished in the University of California system, and he has continued to teach and conduct research at U.C.L.A. Scheibel believes the social custom of retirement may itself be responsible for the loss of frontal-lobe function that we now accept as normal. He notes that research work at the University of California at Berkeley by his wife, Marian Diamond, "has shown that if you stimulate [brain function] you keep it; if you don't, you lose it. One of the worst things we did for high-achieving people was to make them retire. Now we're developing legislative acts to reject this."

At 78 years old, Scheibel is a committed optimist. "In most cases," he says, "aging brings about wisdom." The growing ranks of elderly, he feels, will be "like having a vastly expanded senate in our civilization." We humans will not go gently into a 30-year state of disability and despair. Once we know what the problems are going to be, we will do our best to figure out how to thrive.

Catherine Johnson *of Irvington, N.Y., is co-author with John Ratey of* Shadow Syndromes *(Pantheon, 1997).*

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COMPILED BY EUGENE RAIKHEL

The prospect of living forever, or at least a millennium, has served as a theme for storytellers throughout history. Although writers disagree over whether freedom from death would lead to an enchanted existence, an eternity of boredom and decrepitude—or more likely, some amalgam of the two—few doubt its power to fascinate people. The three excerpts from stories we have chosen (two contemporary, one from the 18th century) imagine how the achievement of a deathless existence, or the attempt to achieve it at all costs, might affect human society as well as the tenor of people's everyday lives.

The Immortal in the Mirror

How would the option of eternal life change the way we view ourselves and the people close to us? In the epilogue to his 1999 book *Time of Our Lives: The Science of Human Aging*, Tom Kirkwood explores these issues through an imagined future in which people are regularly rejuvenated by a technique called fraitching. This technology harnesses the mutability of stem cells, inducing them to migrate to particular parts of the body and brain to replace older cells. Although fraitching has the potential to extend human lives indefinitely, parenthood comes with certain trade-offs that protect society from the perils of a world in which death is a rarity.

Gregor had entered Miranda's life a short time after her ninth fraitch, which, she reflected, would put her in her late 220s. Gregor himself was then nearing his third fraitch, which made him about 150 years her junior. Not that it mattered.

Miranda's love for Gregor had taken her by surprise. It had been immediate and deep, eclipsing the previous loves of her long life. Make no mistake, Miranda's earlier loves had lacked neither warmth nor joy. One of them even resulted in the birth of her cherished son, Nico, now one of her closest friends. But the problem, if problem it had been, was that Miranda had always held something important in reserve.

Holding back from full commitment was a habit conditioned by the boundless possibilities of an unlimited future.

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TATE GALLERY, LONDON/ART RESOURCE, NEW YORK

NANTES TRIPTYCH (1992), BY BILL VIOLA

The only known strategy to cope with this awesome prospect, short of mind-numbing drugs and escapist diversions, was to cultivate and preserve an exaggerated love of oneself. In the early centuries after fraitch technology was developed, the emotional burden of long life was poorly understood and the suicide rate grew alarmingly high. Psychofraitching of the mind quickly became as important as the regeneration of the cells and tissues of the body.

After their first meeting by the river, and during the heady weeks that followed, Miranda had been startled to discover that Gregor loved her with an intensity and passion that went way beyond all of her previous experience. Not short of passion herself, Miranda found her reserve and self-absorption melting away. She delighted in Gregor's presence and he in hers. When Miranda gave up her farmland home to live permanently in the limestone caves where Gregor had carved his beautiful dwelling, her friends were jolted with the shock. With the quaint exception of the Snuggees, a near-invisible sect that inhabited the far north-east and practiced, so it was said, the bizarre habit of "family living," most individuals preferred to live alone, meeting by choice to share bounded periods of time.

Fifteen full and happy years passed quickly in Miranda's and Gregor's lives, their time occupied with creative work and play. During these years, Miranda's love for Gregor had grown ever stronger and deeper, until the day finally came that Miranda made the decision that would alter their lives for ever. Miranda decided that she wanted to share with Gregor the making of a child.

In a world freed from the necessity of aging, the making of children had very great significance. Children were still needed to replace those who died from accidents or suicides, but the accidental

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death rate was so small that their production had to be strictly controlled. The method was simple and stark. Each individual at birth was genetically screened and assigned the right to share in the making of a certain number of children. The usual number was two, but sometimes a smaller number was awarded to limit the spread of harmful genotypes. Exceptionally, a person might be allowed three children if, for example, the recent toll of accidents had been unusually great. The bonus of a third child was awarded by random selection.

To guard against abuse of the quota system and to protect against possible genetic damage to the reproductive cells, which might have a very long wait before use, all fertilizations were carried out in vitro from stored germ cells. Once sufficient germ cells had been removed to cold storage, the gonads were rendered sterile.

To share in the making of a child, a couple would declare their request in a civil ceremony of great solemnity, and following rigorous checks on quota status and genetic compatibility, the fertilization would be performed. The resulting embryo would then be raised to term either within the womb of the mother or, as was increasingly the custom, in fetal incubators.

For a person with a quota of two, like Miranda, the making of a first child was without major consequence. The parents might choose to participate closely in the rearing of the infant, or they might spend only occasional time with their child, as they preferred. They might do so jointly or, more usually, as individuals. A greater preoccupation with self had weakened the traditional bonding of parents with each other and with their child.

In the interests of all, it had become both custom and law that the primary responsibility for the welfare and education of the child rested with the community of which the child would, in due course, become a long-term participant.

However, the making of the final child of a person's quota was an entirely different matter. The birth of this last child signaled the parent's forfeiture of the right to any further fraitches beyond an immediate and final one, at the completion of which a Capsule was implanted. This terminal fraitch delivered the same rejuvenatory effects of the earlier fraitches, but the implanted Capsule imposed a delayed sentence of death. At a random point in time, between 40 and 50 years from the date of implantation, the Capsule would detonate, causing the release of a sequence of neurotoxins that would bring painless death in 5 days. Any attempt at surgical removal of the Capsule would trigger immediate detonation. The bearer of such a Capsule became a Timed One.

It was this fate that Miranda elected for herself when she decided to make a child with Gregor.

THIS MORTAL COIL (1992), BY CHRISTINA HOPE

CHRISTINA HOPE *Superstock*

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Upgrade or Die

The current obsession with aging might pale in comparison with that of a society constructed entirely around the quest for youth, suggests cyberpunk author Bruce Sterling. His 1996 novel *Holy Fire* depicts a time one century from the present, where political power is held by "gerontocrats" and the economy fueled by the "medical-industrial complex." In this world, living longer means taking a gamble on an "upgrade" that might leave you with obsolete hardware.

There were a hundred clever ways to judge a life-extension upgrade. Stay with the blue chips and you were practically guaranteed a steady rate of survival. Volunteer early for some brilliant new start-up, however, and you'd probably outlive the rest of your generation. Keep in mind, though, that novelty and technical sweetness were no guarantees of genuine long-term success. Many lines of medical advancement folded in a spindling crash of medical vaporware, leaving their survivors internally scarred and psychically wrecked.

Medical upgrades were always improving, never steadily, but with convulsive organic jumps. Any blue-chip upgrade licensed in the 2090s would be (very roughly speaking) about twice as effective as the best available in the 2080s....

Given these circumstances, it was wise to postpone your upgrade for as long as

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possible. The longer you waited, the better your choices would become. Unfortunately, the natural aging process never stopped in the meantime, so waiting too long made you subject to serious cumulative damage from natural metabolic decline. Sooner or later you had to hold your nose and make your choice. Since the outcome of leading-edge research was unknown by definition, the authorities could make no guarantees. Therefore, the pursuit of longevity was declared a fundamental freedom left to the choice of the individual. The polity offered its best advice, consensually derived in endless open meetings through vast thriving packs of experts, but advice was nothing better than advice.

If you were smart or lucky, you chose an upgrade path with excellent long-term potential. Your odds were good. You would be around for quite a while. Your choice would become and remain popular. The installed base of users would expand, and that would help you quite a lot. If anything went wrong with your upgrade, there'd be plenty of expertise in dealing with it.

If you were unlucky or foolish, your short-term gains would reveal serious long-term flaws. As the years ground on, you'd become isolated, freakish, obsolescent. The truly bad techniques were the ones that complicated your transitions to another and better upgrade. Once your quality of life was irreparably degraded, you'd have no choice but to turn your attention to the quality of your death.

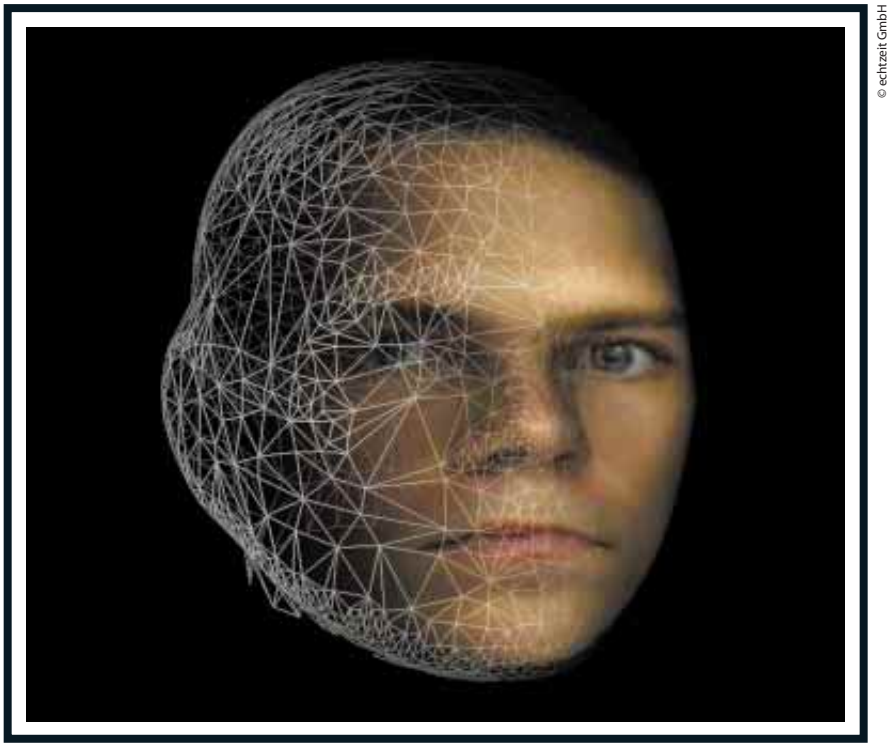
There were various methods of hedging your bets. You could, for instance, be conspicuously and repeatedly good. You always voted, you committed no crimes, you worked for charities, you looked after your fellow citizens with a smile on your face and a song in your heart. You joined civil support and served on net committees. You took a tangible wholehearted interest in the basic well-being of civilization. The community officially wanted you kept alive. You were probably old, probably well behaved, and probably a woman. You were awarded certain special considerations by a polity that appreciated your valuable public spirit. You were the exact sort of person who had basically seized power in modern society.

If you were responsible in your own daily health-care practices, the polity appreciated the way in which you eased the general strain on medical resources. You had objectively demonstrated your firm will to live. Your serious-minded, meticulous approach to longevity was easily verified by anyone, through your public medical records. You had discipline and forethought. You could be kept alive fairly cheaply, because you had been well maintained. You deserved to live.

Some people destroyed their health, yet they rarely did this through deliberate intention. They did it because they lacked foresight, because they were careless, impatient, and irresponsible. There were enormous numbers of medically careless people in the world. There had once been titanic, earth-shattering numbers of such people, but hygienically careless people had died in their billions during the plagues of the 2030s and 2040s. The survivors were a permanently cautious and foresightful lot. Careless people had become a declining interest group with a shrinking demographic share.

Once upon a time, having money had almost guaranteed good health, or at least good health care. Nowadays mere wealth guaranteed very little. People who publicly destroyed their own health had a rather hard time staying wealthy—not because it took good health to become wealthy, but because it took other people's confidence to make and keep money. If you were on a conspicuously public metabolic bender, then you weren't the kind of person that people trusted nowadays. You were a credit risk and a bad business partner. You had points demerits and got cheap medical care.

Even the cheap medical treatments were improving radically, so you were almost sure to do very well by historical standards. But those who destroyed their health still died young, by comparison with the elite. If you wanted to destroy your health, that was your individual prerogative. Once you were thoroughly wrecked, the polity would encourage you to die.



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VIRTUAL HEAD (1999)

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meditations on

quality of life

The Dreadful Prospect

Gerontology, the science of aging, focuses more on improving mental and physical health during the time we've got than on extending our natural life span. And for good reason. To live forever may not be to attain the exalted status of the Greek gods. Long before the advent of the scientific study of the old, Jonathan Swift documented, in his classic account of the Struldbrugs from *Gulliver's Travels,* why an eternity of aging—absent the things that make living worthwhile—may not be something to wish for.

One day, in much good company, I was asked by a person of quality, whether I had seen any of their *Struldbrugs,* or immortals. I said I had not; and desired he would explain to me what he meant by such an appellation, applied to a mortal creature. He told me that sometimes, though very rarely, a child happened to be born in a family with a red circular spot in the forehead, directly over the left eyebrow, which was an infallible mark that it should never die….

I freely own myself to have been struck with inexpressible delight upon hearing this account…. I cried out as in a rapture, "Happy nation, where every child hath at least a chance for being immortal! Happy people, who enjoy so many living examples of ancient virtue, and have masters ready to instruct them in the wisdom of all former ages! But happiest beyond all comparison are those excellent *Struldbrugs,* who, being born exempt from that universal calamity of human nature, have their minds free and disengaged, without the weight and depression of spirits caused by the continual apprehension of death!" …

I enlarged upon many other topics, which the natural desire of endless life and sublunary happiness could easily furnish me with. When I had ended, and the sum of my discourse had been interpreted as before to the rest of the company, there was a good deal of talk among them in the language of the country, not without some laughter at my expense. At last, the same gentleman who had been my interpreter said he was desired by the rest to set me right in a few mistakes, which I had fallen into through the common imbecility of human nature, and upon that allowance was less answerable for them....

After this preface, he gave me a particular account of the *Struldbrugs* among them. He said they commonly acted like mortals till about thirty years old, after which, by degrees, they grew melancholy and dejected, increasing in both till they came to fourscore. This he learned from their own confession: for otherwise, there not being above two or three of that species born in an age, they were too few to form a general observation by. When they came to fourscore years, which is reckoned the extremity of living in this country, they had not only all the follies and infirmities of other old men, but many more which arose from the dreadful prospect of never dying. They were not only opinionative, peevish, covetous, morose, vain, talkative, but incapable of friendship, and dead to all natural affection, which never descended below their grandchildren. Envy and impotent desires are their prevailing passions. But those objects against which their envy seems principally directed, are the vices of the younger sort and the deaths of the old. By reflecting on the former, they find themselves cut off from all possibility of pleasure; and whenever they see a funeral, they lament and repine that others have gone to a harbor of rest to which they themselves never can hope to arrive. They have no remembrance of anything but what they learned and

COURTESY OF LEE JAFFE (www.jaffebros.com/lee/gulliver/)

STRULDBRUGS (1912), BY MILO WINTER

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observed in their youth and middle age, and even that is very imperfect; and for the truth or particulars of any fact, it is safer to depend on common traditions than upon their best recollections. The least miserable among them appear to be those who turn to dotage, and entirely lose their memories; these meet with more pity and assistance, because they want many bad qualities which abound in others.

If a *Struldbrug* happen to marry one of his own kind, the marriage is dissolved of course by the courtesy of the kingdom, as soon as the younger of the two comes to be fourscore. For the law thinks it a reasonable indulgence, that those who are condemned, without any fault of their own, to a perpetual continuance in the world, should not have their misery doubled by the load of a wife. As soon as they have completed the term of eighty years, they are looked on as dead in law; their heirs immediately succeed to their estates; only a small pittance is reserved for their support; and the poor ones are maintained at the public charge. After that period, they are held incapable of any employment of trust or profit; they cannot purchase lands, or take leases; neither are they allowed to be witnesses in any cause, either civil or criminal, not even for the decision of meers and bounds.

SCALA/ART RESOURCE, NEW YORK

TWO HEADS, BY LEONARDO DA VINCI (1452–1519)

At ninety, they lose their teeth and hair; they have at that age no distinction of taste, but eat and drink whatever they can get, without relish or appetite. The diseases they were subject to still continue, without increasing or diminishing. In talking, they forget the common appellation of things, and the names of persons, even of those who are their nearest friends and relations.

For the same reason, they never can amuse themselves with reading, because their memory will not serve to carry them from the beginning of a sentence to the end; and by this defect, they are deprived of the only entertainment whereof they might otherwise be capable.

The language of this country being always upon the flux, the *Struldbrugs* of one age do not understand those of another; neither are they able, after two hundred years, to hold any conversation (farther than by a few general words) with their neighbors the mortals; and thus they lie under the disadvantage of living like foreigners in their own country. This was the account given me of the *Struldbrugs,* as near as I can remember.

The full electronic text of *Gulliver's Travels,* which includes the account of the Struldbrugs in chapter 10, can be downloaded without charge from Project Gutenberg at ftp://metalab.unc.edu/pub/docs/books/gutenberg/etext97/gltrv10.txt on the World Wide Web.

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meditations on

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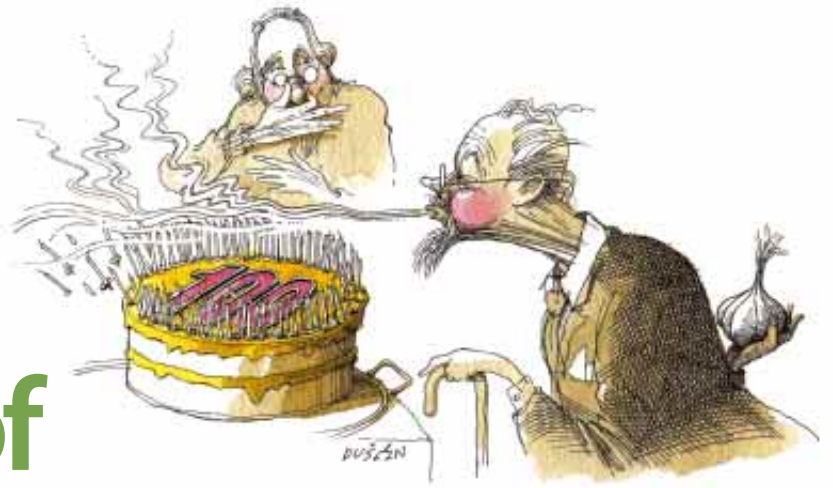

it smells of immortality

BY STEVE MIRSKY

DUSAN PETRICIC

My mother, who turns 39 next year (for the second time), says of her septuagenarian status, "I always wanted to look like Elizabeth Taylor. And now I do." Not everyone is so sanguine about getting older. Some of us fight it tooth and nail, both of which looked whiter and shinier years ago. A friend of mine (really, it's a friend, not me) has embarked on a life-extension regimen that he expects will lead to birthday cakes visible from space. My buddy gets regular aerobic exercise, avoids stress and eats a remarkably healthful diet consisting in great part of steamed vegetables. And garlic.

Garlic does indeed appear to impart a bounty of health benefits. According to published reports, garlic has proved to be good for you in more than 1,000 studies. It seems to cut the risk of various cancers; it lowers blood pressure; it wards off vampires; it lowers cholesterol; it has antifungal properties. It also richly deserves its *nom de fume:* the stinking rose.

My friend, on learning of garlic's health-enhancing powers, replaced the apple with a clove of garlic in the old proverb regarding methods to keep the doctor away. He then extrapolated that if one clove per day was good, two or three might be even better. I saw him recently for the first time in weeks. As soon as I entered his apartment, the fragrance slammed me. As I got close to him, my eyes began to water. I instinctively (emphasis on the "stinct") covered my nose with the back of my hand. "How many today?" I asked. "Seven!" he replied proudly. I struggled for oxygen and muttered during an exhalation, "Well, you'll never get an infection, that's for sure. No one's ever going to get close enough." Sitting in his apartment, I slowly got somewhat used to the rich bouquet that was making me a bit queasy and light-headed. I took a few sips of what I would have taken to be ordinary tap water but was in fact distilled, from his new home water distiller.

We soon left for a drive, during which we stopped at a local natural foods store to pick up some supplies. (Apparently, I'm a health-food enabler.) While my friend wandered, presumably examining the latest in garlic presses and garlic supplements, I perused the soy goods. Years ago I wrote a story about the possible benefits of soy and convinced myself that there was enough basic research on its anticancer and cholesterol-lowering powers to make a few of the bean's products a small part of my diet. I spotted and bought some soy-based vegetarian pepperoni. A few hours later I adulterated a perfectly respectable slice of Bronx-made Sicilian-style pizza with thin slices of same soy. Though not terrible, it wasn't real pepperoni. And it probably won't happen again.

After stopping at my house for a while, we prepared to get back in the car. I then noticed that he had never taken off a pair of thin glove liners while in my home. Now, I admit to being a lousy housekeeper—like nature, I abhor a vacuum—but I don't think the place is actually dangerous. "You don't want to touch anything here, do you?" I asked. He said, "No, I'm just chilly," which may be true now that his body-fat levels are down to the point where even his nerve cells are probably losing their insulation. But the sheepish grin on his face convinced me that at least part of the issue might be mysophobia (which sounds like fear of soy soup but is actually dread of germs). "Listen," I said, "I have one question. How you gonna keep those gloves on when your fingernails are two inches long, Howard Hughes?"

My friend could have the last laugh. I may be long dead when he is still steaming broccoli, distilling water and, of course, gobbling garlic. But I figure, based on genes and my more moderate but still relatively healthy lifestyle, that I have a solid 85 years in store, maybe more. And I swear to you, a good slice of Bronx-made Sicilian pizza really is to die for.

STEVE MIRSKY is an editor and columnist at Scientific American.

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